United States Senate Committee on Health, Education, Labor and Pensions

Emergence of the Superbug: Antimicrobial Resistance in the U.S.

Written Testimony of

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Mr. Chairman, Ranking Member, and Members of the Committee, thank you for the opportunity to testify before you today about the need to develop and implement comprehensive policy initiatives to address the public health impacts of antimicrobial resistant bacterial infections.

I am Dr. Barry Eisenstein, Senior Vice President of Scientific Affairs at Cubist Pharmaceuticals. Cubist is a biopharmaceutical company focused on the research, development and commercialization of pharmaceutical products that address unmet medical needs in the acute care environment. Headquartered in Lexington, Massachusetts, we currently market CUBICIN® (daptomycin for injection), the first intravenous (IV) antibiotic from a class of anti-infectives called lipopeptides. CUBICIN received FDA approval for the treatment of complicated skin and skin structure infections caused by certain susceptible strains of Gram-positive microorganisms, including methicillin-resistant *Staphylococcus aureus* (MRSA). CUBICIN is also approved in the U.S. for the treatment of *S. aureus* bloodstream infections (bacteremia), and is the only IV antibiotic approved for this indication based on the results of a prospective, randomized, controlled registration trial. In the wake of a highly successful launch of CUBICIN, the company has a growing early stage pipeline of programs which can leverage Cubist's scientific, clinical and regulatory expertise as well as its proven infectious disease and acute care commercial organization.

As Senior Vice President of Scientific Affairs, I am responsible for leading the efforts at Cubist to understand the medical needs best answered by Cubicin, to interact with leading scientists and health care providers in the United States and elsewhere, and to advise our scientific staff regarding ongoing needs related to infectious diseases, particularly those due to resistant bacteria. I am trained in internal medicine, infectious diseases, and microbiology. I

have been a hospital epidemiologist, chief of an Infectious Diseases division, chair of an academic department of microbiology and immunology, the leader of infectious diseases discovery and clinical development at a major pharmaceutical company, and am presently, in addition to my job at Cubist, Clinical Professor of Medicine at Harvard Medical School, where I teach. I hold leadership positions with the Infectious Diseases Society of America, the National Foundation for Infectious Diseases, and the American Society for Microbiology, and am currently an editor of the journal, Antimicrobial Agents and Chemotherapy. I have been studying antibiotic resistance and treating patients with infectious diseases for over three decades, have edited major textbooks, and published over 100 scholarly articles in the field.

Antimicrobial Resistance: A Public Health Threat

During the last several decades, the prevalence of antimicrobial resistant organisms in U.S. hospitals and medical centers has increased. According to 2002 data from the Centers for Disease Control and Prevention (CDC), more than 1.7 million people acquire bacterial infections in U.S. hospitals each year, and 99,000 die as a result. CDC estimates that up to 70 percent of those bacterial infections are resistant to at least one drug, at a cost of approximately $5 billion annually[1]. A recent study published in the Journal of the American Medical Association (JAMA), extrapolated data from nine U.S. communities to estimate that there were 94,360 invasive MRSA infections alone in the U.S. in 2005 which resulted in 18,650 deaths[2]—to say nothing of the prevalence of other drug resistant infections. Antimicrobial resistance is increasingly a public health threat: patients who contract a resistant infection require more days of antimicrobial therapy than patients who do not; require more days in the hospital than those who do not; and generally face worse outcomes than those who do not[3]. We must implement effective measures to combat antimicrobial resistance.

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[1] Centers for Disease Control and Prevention *at* http://www.cdc.gov/ncidod/dhqp/ar.html.

[2] R.M. Klevens et al., *Invasive Methicillin-Resistant* Staphylococcus aureus *Infections in the United States*, JAMA, 2007;298:1763-1771.

[3] A. Shorr et al., *Bacteremia Due to* Staphylococcus aureus: *Acquisition, Methicillin Resistance, and Treatment Issues*, Medscape Clinical Review, October 2004; M.A. Abramson, D.J. Sexton, *Nosocomial Methicillin-Resistant and Methicillin Susceptible Staphylococcus aureus Primary Bacteremia: At What Costs?"* Infection Control and Hospital Epidemiology, 1999;20:408-411.

Unfortunately, given the rapid evolution of bacteria, development of antibiotic resistance is almost inevitable, thus policy efforts to address antimicrobial resistance must focus on: 1) adoption and maintenance of practices that reduce the rates of transmission of resistant infections; 2) appropriate use of existing antimicrobials to delay development of resistance; and 3) implementation of incentives to encourage the continued research and development of new antimicrobials to ensure, to the extent possible, a steady supply of effective drugs.

Lack of Effective Antimicrobials is Reaching a Crisis Point

My testimony today will focus on suggestions for incentives to encourage innovative antimicrobial research and development (R&D). We are approaching a "crisis point" with antimicrobial resistance and lack of new therapies, particularly against gram negative bacteria, (e.g., *Acinetobacter*, which is infecting both intensive care patients in American hospitals and our troops in the Middle East conflicts at alarming rates and which is often untreatable[4]). Among the gram positive bacteria, the disturbing rates of MRSA and the emergence of vancomycin-resistant enterococci (VRE) increasingly leave infectious disease doctors with few, if any, effective therapies for certain strains of bacterial infection.

Overuse and misuse of antibiotics has contributed to the development of resistance and has left hospital shelves increasingly barren of effective antimicrobial therapies. In addition, as a class of drugs, antibiotics face unique therapeutic challenges, which other treatments do not encounter. As I mentioned above, bacteria evolve so quickly that development of resistance is inevitable and thus each new antibiotic is a "wasting asset." In other words, each therapy has a finite period of time during which it will be effective. For example, the discovery of penicillin in 1928 was nothing short of a medical miracle. Yet only four years after the drug became widely commercially available during World War II, reports of resistant microbes began emerging. This has far reaching consequences for patients and physicians who may be left without therapeutic options, but it also impacts the willingness of industry to invest in antimicrobial R&D as newer agents effective against the most important antibiotic-resistant pathogens, like MRSA, are often viewed as niche products to be used highly selectively by practicing physicians.

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[4] L.L. Maragakis and T.M. Perl, Acinetobacter baumannii: *Epidemiology, Antimicrobial Resistance, and Treatment Options*, Clinical Infectious Diseases, 2008;46:1254-1263.

Industry's hesitancy to invest in antimicrobial development is compounded by the consequences of the depreciating nature of antimicrobials—when faced with the reality that antibiotics have a finite lifespan, health care providers engage in the practice of optimizing antibiotic utilization ("antibiotic stewardship"). While this can result in more appropriate use of antimicrobials through measures that limit exposure to antibiotics (e.g., prescribing antibiotics only when necessary, effectively using diagnostic techniques to select the most appropriate antibiotic, and acquiring appropriate culture and sensitivity data to ensure suitable dosing), it can also result in physicians simply reserving the newest antibiotics for use only as a last resort in the most difficult-to-treat cases[5]. This apparent virtue of preserving antibiotics (i.e., helping the "demand side") paradoxically hurts the "supply side" by making commercial return on these antibiotics more difficult to realize, thereby causing economic disincentives for industry to engage in cutting edge antimicrobial R&D. The consequence is loss rather than gain in the antibiotics armamentarium, a fact not well appreciated by practicing physicians or by some proponents of antibiotic stewardship[6].

Finally, antimicrobials are used in acute settings, for limited timeframes (7-10 days), rather than daily for the life-time of the patient, as with treatments for chronic diseases, making it difficult to rely on commercialization of an antimicrobial as a steady source of financial returns.

In addition to challenges inherent to antibiotics as a class of drugs (emergence of resistance, prescribing habits, and resulting antimicrobial stewardship), over the last decade, regulatory uncertainty, including impractical and changing FDA guidelines has had a significant negative impact on approval of antibiotics. According to Extending the Cure, 14 classes of antibiotics were introduced for human use between 1935 and 1968; since then only five have been introduced[7]. While many factors, as discussed above, have contributed to this decline,

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[5] K. Kaye et al., *The Deadly Toll of Invasive Methicillin-Resistant* Staphylococcus aureus *Infection in Community Hospitals*, Clinical Infectious Diseases, 2008;46:1568-1577.

[6] R. Laxminarayan and A. Malani, *Extending the Cure: Policy Responses to the Growing Threat of Antimicrobial Resistance* (2007), *available at* http://www.extendingthecure.org/research_and_downloads.html.

[7] *See*, Extending the Cure, *Policy Responses to the Growing Threat of Antibiotic Resistance, Policy Brief 6: The Antibiotic Pipeline*, May 2008, *available at* http://www.extendingthecure.org/downloads/policy_briefs/Policy_Brief6_May08_newdrugs.pdf.

unpredictable approval requirements and timelines only add to already existing economic disincentives for industry to invest in antimicrobial R&D[8].

Taken together and without further incentives to encourage investment in antimicrobial development, both big and small pharmaceuticals and biotechnology companies have already begun limiting their R&D investment in anti-infectives, preferring instead to focus on other, more financially certain therapeutic areas. The consequences of this lack of antimicrobial R&D has become devastating for patients, leaving us with increasing rates of antimicrobial resistance and fewer and fewer available therapies[9].

Support for Ongoing Initiatives to Combat Antimicrobial Resistance

Cubist supports several ongoing initiatives at the Department of Health and Human Services (HHS) to effectively address antimicrobial resistance, and encourages HHS to continue to work toward completion of these programs, including:

(1) Activities of the Food and Drug Administration (FDA) to implement sections of the Food and Drug Administration Amendments Act (FDAAA) (Pub. L. No. 110-85).

Specifically, Cubist is pleased that the FDA issued a draft guidance outlining the agency's proposed procedures for complying with section 1111 of FDAAA, which requires the FDA to periodically review and update antibiotic "breakpoints." An antibiotic breakpoint is the dosing concentration (mcg/mL) after which the drug is no longer considered clinically effective. Breakpoints are critical because they determine bacterial resistance. During antibacterial susceptibility testing to identify which antibiotics will kill or inhibit the growth of the isolated bacterial culture, if the bacteria are not inhibited at the "breakpoint" concentration, it is considered resistant.

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[8] *See,* Docket No. FDA-2008-N-0225-008.1 and -008.2, Comments of the Infectious Diseases Society of America, *available at* http://www.regulations.gov/fdmspublic/component/main?main=DocketDetail&d=FDA-2008-N-0225.

[9] See, *Bad Bugs, No Drugs: As Antibiotic Discovery Stagnates…A Public Health Crisis Brews*, Infectious Diseases Society of America, July 2004, *available at* http://www.idsociety.org/WorkArea/showcontent.aspx?id=5554; G.H. Talbot et al., *Bad Bugs Need Drugs: An Update on the Development Pipeline from the Antimicrobial Availability Task Force of the Infectious Diseases Society of America*, Clinical Infectious Diseases, 2006;42:657-668; B. Spellberg et al., *The Epidemic of Antibiotic Resistant Infections: A Call to Action for the Medical Community from the Infectious Diseases Society of America,* Clinical Infectious Diseases 2006;42:155-164.

Cubist, as well as the Infectious Diseases Society of America and the Clinical Laboratory Standards Institute believe that the breakpoints included in the labels of many older antibiotics do not reflect emerging resistance. Thus these labels are outdated, compromising physicians' ability to appropriately and effectively treat patients, often giving them a false sense of confidence about an older antibiotic, like vancomycin[10]. We are pleased that the FDA has already revised the label for vancomycin injection to reflect a breakpoint of 2 mcg/ML against *Staphylococcus aureus*.

However, while we appreciate this first step by the FDA, many in the infectious disease community, including academic and clinical experts, feel that even this lower breakpoint for vancomycin does not reflect true clinical resistance to the drug, putting patients at serious risk of receiving ineffective treatment. To quote from a recent paper on the topic:

> "it is becoming clear that vancomycin is losing potency against *S. aureus*, including MRSA. Serious infections due to MRSA defined as susceptible in the laboratory are not responding well to vancomycin. This is demonstrated by increased mortality seen in patients with MRSA infection and markedly attenuated vancomycin efficacy caused by vancomycin heteroresistance in *S. aureus*. Therefore, it appears that our definition of vancomycin susceptibility requires further scrutiny as applied to serious MRSA infections, such as bacteremia and pneumonia."[11]

This apparent reluctance by the FDA to apply current standards of measuring resistance to older antibiotic compounds is one of the most significant economic disincentives to industry investment in R&D, as well as a s significant barrier to state-of-the art patient care. We encourage FDA to lower the vancomycin breakpoint and to continue to be vigilant in monitoring the efficacy of it and other antibiotics, as required under FDA Section 1111.

Cubist also appreciates that the agency convened a public meeting on April 28, 2008 as required by section 1112 of FDAAA, to discuss and debate measures to

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[10] G. Sakoulas and R.C. Moellering, Jr., *Increasing Antibiotic Resistance among Methicillin-Resistant* Staphylococcus aureus *Strains*, Clinical Infectious Diseases, 2008;46:S360-S367.

[11] G. Sakoulas and R.C. Moellering, Jr., *Increasing Antibiotic Resistance among Methicillin-Resistant* Staphylococcus aureus *Strains*, Clinical Infectious Diseases, 2008;46:S360-S367. *See also*, I.M. Gould, Editorial, *The Problem With Glycopeptides*, International Journal of Antimicrobial Agents 30 (2007):1–3.

combat antimicrobial resistance. We hope the FDA will strongly consider some of the suggestions offered at this meeting[12].

(2) Implementation of the Hospital Acquired Condition (HAC) rule, by the Centers for Medicare and Medicaid Services (CMS) as a measure to encourage hospitals to engage in proven, evidence-based behavior to prevent the transmission of hospital acquired infections, including resistant bacterial infections.

In the development of these policies, it is critical for CMS to be mindful of the challenges that hospitals face in detecting and preventing conditions that are often considered hospital acquired. Due to factors outside the control of hospitals, certain conditions are not reasonably preventable. In those circumstances, payment policies based on the presumption that hospitals can prevent these conditions from occurring will not produce the desired results and could impact quality of care. CMS must take these factors into account as it implements the HAC provisions. For example, while many infections are preventable through proper hospital protocols and safety measures, data has shown that hospitals lack the ability to reasonably prevent infections caused by MRSA. Individuals can become colonized with MRSA in the community as well as in health care settings, and while hospitals can take steps to prevent MRSA from spreading between patients in the hospital setting, they cannot reasonably prevent a patient who is colonized with MRSA from developing an active infection in the hospital setting.

(3) Efforts by Congress to extend Medicare coverage for home infusion to include ancillary services associated with home administration of IV drugs, including antibiotics.

Home infusion would allow patients in need of antibiotic treatment, including those with MRSA or other resistant bacterial infections, to administer the drug themselves, in a non-hospital setting. However, in contrast to many private insurance plans, Medicare does not cover necessary services related to home administration of injectable drugs, such as the supplies, nursing services or equipment. This lack of coverage prevents many Medicare

[12] *See e.g.*, Docket No. FDA-2008-N-0225-0011, Comments of the Clinical Laboratory Standards Institute, *available at* http://www.regulations.gov/fdmspublic/component/main?main=DocketDetail&d=FDA-2008-N-0225.

beneficiaries from taking advantage of these services and forces these patients to remain in the hospital longer than necessary simply to receive their antibiotics. Extended hospital stays are costly, inconvenient, and most importantly, compromise the health of other patients who are at risk of contracting the resistant bacterial infection from their neighbors. We encourage Congress to extend Medicare coverage to include home infusion services as one measure to improve patient care and reduce unnecessary transmission of MRSA and other bacterial infections. Extension of Medicare coverage would also open additional markets for IV antibiotics, providing an incentive to industry to engage in antibiotic R&D.

Additional Suggested Policy Proposals

In addition to working toward the achievement of the ongoing initiatives described above, Cubist also believes that to directly address the unique barriers to industry investment in innovative antimicrobial research and development, Congress should enact additional incentives which will encourage such research. Specifically, Cubist proposes the following options:

(1) Establish research and development tax credits for antimicrobials, modeled after bills introduced by Senator Schumer and Representative Towns.

By allowing innovative companies a tax credit equal to a percentage of their expenses devoted to research and development of "qualified" products (e.g., antimicrobials and antivirals), such expenses, which can run as high as $1 billion to bring a drug to market, are mitigated, thus incentivizing industry to devote more time and resource toward the research and development of these critical new products. To ensure that the tax credit encourages research and development of innovative new products, rather than reformulations or variations on already existing drugs or diagnostics, the credit could be limited to research on new molecular entities or new diagnostics. The federal government, as well as several states (including Massachusetts) have in place broader R&D tax credits to encourage job creation and cutting edge pharmaceutical research. However, a federal R&D tax credit specific to antimicrobials and similar qualified products would focus pharmaceutical and biotech R&D on meeting unmet antibiotic medical needs for patients.

(2) Encourage the CDC and the Department of Homeland Security to stockpile antibiotics in the Strategic National Stockpile; similarly encourage hospitals to "stockpile" antimicrobials.

The federal Strategic National Stockpile (SNS) is managed jointly through the Department of Homeland Security and the Department of Health and Human Services. The SNS is housed at CDC and has large quantities of medicine and medical supplies to protect the public if there is a public health emergency and local supplies run out. Certain antimicrobials are already stockpiled by the SNS, as well as other medical countermeasures, but this list could be expanded to include additional categories of antimicrobial products effective against resistant pathogens. While the SNS is primarily designed to ensure sufficient public access to life-saving medicines in the event of an emergency, by advance purchasing in large quantities certain drugs and biologics, the SNS also incentivizes the research and development of such products. Similarly, if hospitals were encouraged to stockpile or enter into advanced purchase contracts for antimicrobials for use against resistant infections, this would encourage much needed antimicrobial R&D.

(3) Create infectious disease product development grants modeled on FDA's successful orphan product development (OPD) grants and provide additional 7 years of exclusivity for certain antimicrobial products.

Orphan development grants are intended to encourage clinical development of products for use in rare diseases or conditions. They are authorized under current law, and could include antimicrobials, if certain infectious diseases meet the statutory criteria for a "rare disease." In fact, under section 1112 of FDAAA, FDA was directed to (and did) hold a public meeting to consider which infectious diseases would be considered "rare diseases", and thus which products would be eligible for OPD grants. In addition to the OPD grants, these antibiotics should be eligible for orphan drug status and the associated seven year period of exclusivity to stimulate innovation and provide an adequate return on investment. The lengthened exclusivity would also take into account the unique, slow uptake of new antibiotics into the marketplace based on the usual practices of antibiotic stewardship. (By contrast there is no such delay in the use of the newest life-saving cancer drugs, which, like antibiotics, work by ridding the patient of noxious, life-threatening cells.)

In the alternative to including antimicrobials/infectious diseases under the umbrella of orphan drug grants, similar to the OPD grants, Congress could authorize grants specifically directed at antimicrobials and other infectious disease products. Like the orphan product grants, grants for infectious disease product development would focus targeted federal dollars in an area of critical public health need but limited commercial potential. Additional exclusivity could also be granted for these products upon approval if certain criteria were met.

(4) Continue utilizing rapid approval mechanisms at FDA, such as Fast Track and Priority Review; expand the FDAAA Tropical Disease Priority Review voucher system to additional categories of antimicrobials.

FDA "Fast Track" designation (requested by the sponsor) is a process designed to facilitate the development, and expedite the review of new drugs or biologics indicated to treat serious or life-threatening diseases and which fill an unmet medical need. "Priority Review" is one of two review designations for a product. To hasten approval of drugs or biologics that offer major advances in treatment, FDA designates such drugs, at the request of the sponsor, as Priority Review drugs. The goal for FDA premarket review of a Priority Review drug is six months, compared to ten months for standard review drugs. Antibiotics which are indicated to treat serious or life-threatening diseases, or which provide major advances in treatment are eligible for Fast Track or Priority Review. Cubist encourages product sponsors and the FDA to effectively utilize these approval options.

In addition, to encourage sponsors to engage in innovative antimicrobial R&D, Congress could expand the tropical disease priority review voucher system enacted under FDAAA to include additional categories of antimicrobials (e.g., those that are indicated for serious or life threatening diseases). The FDAAA provision establishes a system of rewarding priority review vouchers to sponsors who file an NDA for a drug indicated for the treatment or prevention of a tropical disease. The priority review voucher entitles the holder of the voucher to priority review of a single new human drug or biologic application (separate from the NDA for the tropical disease product) and is transferable. Extension of the provision to include other categories of antimicrobials would provide additional

incentives for industry to engage in cutting edge R&D.

(5) Provide additional regulatory guidance at FDA for approval of antimicrobials.

In addition to expediting approval times through Fast Track and Priority Review, to address the increasing regulatory uncertainty antimicrobial sponsors face when submitting a new antibiotic for approval, the agency should clarify approval requirements and reestablish consistency, predictability and timeliness in premarket review of antimicrobials. This should include release and periodic review of the guidance on conduct of antimicrobial clinical trials, as required by section 9111 of FDAAA, as well as careful review and consideration of the GAO report required by section 1114 of FDAAA examining how certain FDAAA provisions related to antibiotics have encouraged development of new antibiotics.

(6) Authorize study and establishment of guaranteed market contracts and other "pull" mechanisms.

Apart from the SNS discussed above, HHS could create advance purchase commitments or other "promised market" mechanisms (e.g., an antimicrobial purchase fund) to encourage the development of future antimicrobials. Guaranteed contracts in small amounts (less than $50-$100 million) could provide an important market foundation to focus hospital, private payor and physician attention to novel therapies.

(7) Establish a Commission on Infectious Diseases Product Development, modeled after legislation introduced by Reps. Baird and Cubin, to increase public-private development collaboration.

The Beating Infections through Research and Development Act (H.R. 1496) requires establishment of a Commission on Infectious Disease Product Development to identify the most dangerous infectious disease pathogens that are or are likely to become a danger to public health. Establishment of such a commission would be beneficial in directing limited R&D resources to the most critical areas of need. The Commission should include members of relevant government agencies, including the Department of Health and Human Servicse, the Food and Drug Administration, CDC, the Department of Homeland Security, and the Department of Defense, as well as pharmaceutical and biotechnology companies, venture

capital firms, financiers, and other experts in the economics of drug development. Public sessions and hearings of the Commission should be mandated to explore the issues of unmet need as well as different mechanisms to better encourage the development of innovative antimicrobials.

(8) Authorize federally-guaranteed loans for product development and infrastructure.

Congress could authorize small business or targeted Business and Industry (B&I) Guaranteed Loans similar to those administered by the USDA Rural Business-Cooperative Service (RBS) and the Small Business Administration (SBA) Certified Development Company (504) Loan Program. These programs offer such maximum loan sizes of as $25 million with 30 year terms at market advantageous rates. Loans would serve to reduce small, startup companies' reliance upon venture capital, and could encourage them to innovate creatively on therapeutically significant, potentially higher risk development projects. Loans amounts up to $25 million would serve to advance drug candidates up to clinical investigation (IND stage); additional amounts would be required for early clinical trials.

Conclusion

Thank you for the opportunity to testify today. Antimicrobial resistance is a very real threat to public health and one that is only getting worse. I urge Congress to strongly consider the suggestions I, and others, have offered as steps toward managing emergence, transmission, and treatment of drug resistant organisms.