Committee on Energy and Commerce
Subcommittee on Health
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Hearing on
"Promoting the Development of Antibiotics
and Ensuring Judicious Use in Humans"

Written Testimony of
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Chairman Pallone, Ranking Member Shimkus, and Members of the Subcommittee, thank you for the opportunity to testify on the urgent need to spur greater innovation and accelerate the development of new therapeutics to combat the threat 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 – especially antibiotics -- 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 in 2003 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 pipeline that includes antibiotic candidates for difficult to treat infections including *Clostridium difficile* and serious Gram-negative infections, including those caused by multi-drug resistant *Pseudomonas aeruginosa*.

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 unmet medical needs in the area of 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 or have held 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

Fostering Innovation is an Essential Solution Against Antimicrobial Resistance

Mr. Chairman, I commend you and the Subcommittee for pursuing this important public health issue. You have recently received testimony from the leaders of the Centers for Disease Control and Prevention (CDC), the National Institutes of Health (NIH) and, today, the Food and Drug Administration (FDA), echoing numerous independent studies and reports from organizations like the London School of Economics, Extending the Cure and the Infectious Disease Society of America (IDSA) that concur upon the increasing severity of the threat of antibiotic resistance. I would like commend IDSA, in particular, for their recent launch of the 10x'20 Initiative. The Initiative calls on the U.S. and other governments to partner globally – with public and private entities alike – to develop ten new antibiotics by 2020.

These agencies, experts and think tanks are unanimous: the risks to public health at home and abroad are great and the gaps in our medical preparedness and our therapeutic options are not only substantial, but also growing with every passing month.

We are approaching a "crisis point" with antimicrobial resistance and lack of new therapies against gram positive bacteria such as "staph" and gram negative bacteria such as *Acinetobacter*. 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.

Mr. Chairman, you yourself noted in the Subcommittee's last hearing on this topic that gram negative infections like *Acinetobacter* have been a significant issue for our troops returning from the Middle East. Many servicemen and servicewomen have been inflicted with these infections at alarming rates and are often untreatable[4]. A 2006 study found that as many of 89 percent of sample infections were resistant to at least three classes of antibiotics and 15 percent were resistant to all nine antibiotics screened[5]. The *Los Angeles Times* noted that these infections have spread beyond Walter Reed to other military hospitals[6].

Overuse and misuse of antibiotics has contributed to the development of resistance and has left hospital shelves increasingly barren of effective antimicrobial therapies.

Three years ago, we encouraged this Subcommittee to ask the FDA whether the incentives available under the Orphan Drug Act, which have so successfully driven innovation against rare diseases, might also be made available to promote development of new antimicrobial drugs. With the leadership of this Subcommittee, a provision of the Food and Drug Administration Amendments Act of 2007 (FDAAA, Pub. L. No. 110-85) was enacted that called on FDA to convene a public meeting and determine whether the Orphan Drug Act could be

applied in this manner. Regrettably, the Agency concluded that they cannot under the law as written.

Two years ago, I testified before your colleagues on the Senate Committee on Health, Education, Labor and Pensions that we are facing a "crisis point" in our medical arsenal against resistant infections. Since then, public and clinical awareness of the threats we face has grown. Government authorities and health care decision-makers have taken some steps to better respond to these threats. The Patient Protection and Affordable Care Act (PPACA, Pub. L. No. 111-148) took marginal steps, addressing the quality of inpatient care and hospital-acquired infections, and creating a modest, short-term incentive called the Qualifying Therapeutic Discovery Project Tax Credit.

But today, Mr. Chairman, I can report that much more remains to be done and the urgency is greater than ever. Congress and the Administration must make additional, specific improvements in federal law and policy before we can achieve greater progress against resistant infections. That is why Cubist strongly supports enactment of H.R.2400, the Strategies to Address Antimicrobial Resistance (STAAR) Act. The STAAR Act would enhance research, improve federal coordination, and expand data collection against the threat of antimicrobial resistance.

But even these steps will not foster innovation and the development of new antimicrobial drugs. The STAAR Act does not include provisions that would directly encourage development of new therapeutics. That is why Congress and the Administration should take immediate additional steps on consensus recommendations that already exist to promote the research and commercialization of new drugs, diagnostics and vaccines against resistant infections. These recommendations, like mine today, are clear, simple and actionable. I urge the Subcommittee to take action on them as soon as possible.

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* 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. 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

As a class of drugs, antibiotics face unique therapeutic challenges, which other treatments do not encounter. Bacteria evolve so quickly that development of resistance is inevitable and thus each new antibiotic is a "wasting asset" with 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 profoundly and adversely 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.

Industry's reluctance to invest in antimicrobial development is compounded by 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 (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[7].

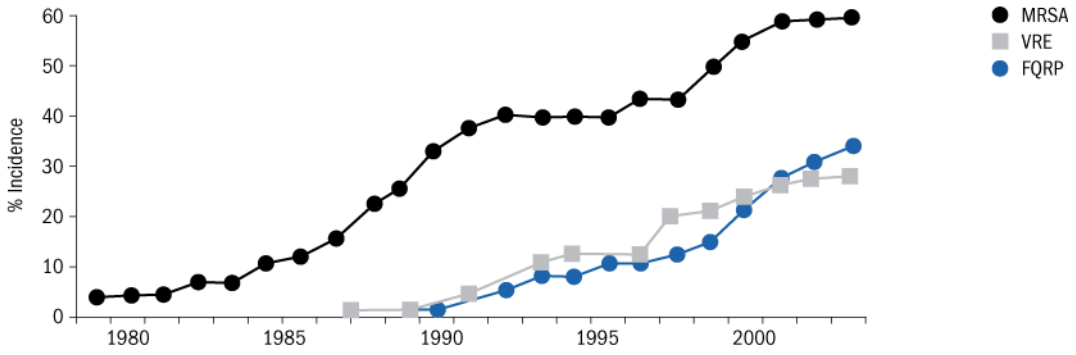
Yet this appropriate goal of preserving antibiotics paradoxically hurts the "supply side" of a pharmaceutical manufacturer's potential market by making commercial return on these antibiotics more difficult to realize. This is a critical economic disincentive for industry to engage in cutting edge antimicrobial 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[8].

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 even more 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 ever-shifting 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[9]. While many factors, as discussed above, have contributed to this decline,

unpredictable approval requirements and timelines only add to already existing economic disincentives for industry to invest in antimicrobial R&D[10].

These well-documented features of the antimicrobial market are identified time and again by economists, analysts, and independent think tanks as the reasons why both big and small pharmaceuticals and biotechnology companies have largely fled from R&D investment in anti-infectives, preferring instead to focus on other, more financially certain therapeutic areas. A recent analysis published in *Clinical Infectious Diseases* (CID) found only five new antibiotics in the R&D pipeline out of more than 506 drugs in development. By comparison, pharmaceutical companies were developing 67 new drugs for cancer, 33 for inflammation/pain, 34 for metabolic/endocrine disorders, and 32 for pulmonary disease. The CID analysis found that FDA approvals of new antibiotics declined 56 percent during the past 20 years (1998-2002 versus 1983-1987). The consequences of this lack of antimicrobial R&D have become devastating for patients, leaving us with increasing rates of antimicrobial resistance and fewer and fewer available therapies[11].

Figure 1. The emergence of antimicrobial-resistant bacteria over time[12].



MRSA=methicillin-resistant *Staphylococcus aureus*; VRE=vancomycin-resistant enterococci; FQRP=fluoroquinolone-resistant *Pseudomonas aeruginosa*.

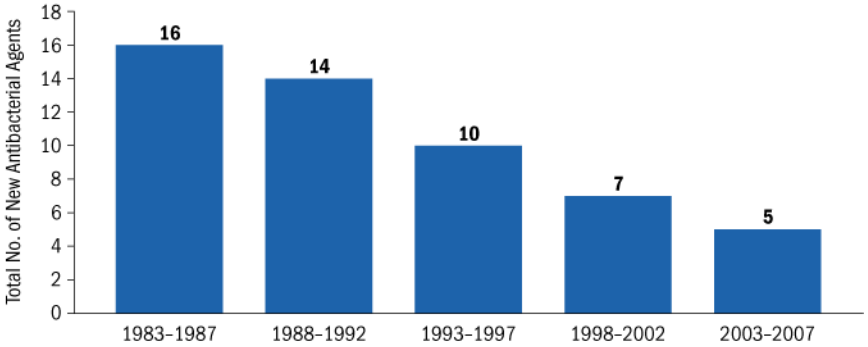


Figure 2. FDA approval of new antibiotics has decreased by 70% since the mid-1980s[12].

Proven Incentives Exist to Encourage Antimicrobial Innovation

As one of the few American biopharmaceutical companies primarily focused on the discovery and commercialization of novel anti-infectives, Cubist has unique insight into the market and regulatory barriers to innovative antimicrobial research and development. We believe that specific policies that have worked successfully to correct similar market failures in rare diseases, pediatric drug use, and medical countermeasures, can and should be applied by Congress and the Administration to the "dry pipeline" of antibiotics and antimicrobials.

We believe it is critical that Congress consider policies that will not only help sustain companies like Cubist already engaged in the full spectrum of drug discovery, from molecular discovery to animal studies through complex, multicenter pivotal human trials, but also attract new entrants – large and small - into this critical therapeutic area. We urge you to keep in mind the high risks, extraordinary expense, and unpredictability of the research and development that are entailed in bringing a new antibiotic to market. For these reasons, new incentives must be designed so that they encourage investment in activities across the research spectrum, from basic research to clinical trials, and target as broad a range of scientists, entrepreneurs, large and small companies, and life science investors as possible.

With these thoughts in mind, Cubist respectfully recommends consideration of the following options, in order of their importance and potential beneficial impact:

(1) Enhance market and data exclusivity for qualified infectious disease products.

In the past, Congress has successfully corrected other pharmaceutical market failures and promoted robust innovation through extensions of exclusivity. Tremendous progress has been achieved in reversing the absence of investment and R&D in rare diseases through the Orphan Drug Act, as well as the pediatric uses of medicines through the availability of 6-month pediatric exclusivity. As I mentioned earlier, this Subcommittee and Congress recently explored the possibility of applying Orphan Drug Act exclusivity to novel antimicrobials. Applying this proven, effective incentive to this narrow and well-documented market failure would send a

strong signal to scientists, entrepreneurs, venture capitalists, and the markets, and greatly encourage more R&D and commercialization of new drugs to treat resistant infections.

Recognizing that our greatest concern must be to foster and maintain effective treatments against resistant infections in humans (and not in animals), I encourage the Subcommittee to consider linking any extension of exclusivity for novel antimicrobials to an assurance that the qualified novel agent be prescribed responsibly for human use only.

(2) Exempt qualified infectious disease products from the pharmaceutical excise tax and 340B drug discount expansion enacted under PPACA.

Under PPACA, pharmaceutical manufacturers are required to pay an excise tax based upon a sliding scale of branded prescription drug sales for the preceding calendar year, in proportion to the relevant sales of all manufacturers. Yet Congress exempted orphan drugs from these calculations to maintain, as much as possible, the financial incentives to pursue development of these important therapeutics. Similarly, PPACA expands the scope of covered entities eligible for drug discounts on the purchase of outpatient drugs available under section 340B of the Public Health Service Act, but also exempts drugs with orphan designations from the FDA from this expansion for the newly eligible covered entities. Expanding these limited exemptions from the excise tax and the 340B discount expansion to qualifying infectious disease products would create highly visible financial incentives to pursue their development.

(3) Authorize the study and establishment of guaranteed market contracts and other "pull" market mechanisms, as well as the use of "other transactions" authority of HHS.

Last year, the London School of Economics published a report on incentives to promote innovation in antimicrobial therapeutics. The report was commissioned by the Swedish government in its capacity of the European Union Presidency. Among those incentives studied were market "pull" mechanisms, such as monetary prizes and advance market commitments, which serve as general incentives to drug development, encouraging pre-clinical and clinical development through a pre-commitment of donors to buy an effective antimicrobial if and when it is actually developed, and when its efficacy is established and confirmed by an appropriate regulatory authority. Additionally, under 10 U.S.C. § 2371, the Department of Defense (DoD) employs statutory authority to develop highly flexible "other transactions" contractual instruments that are different from procurement contracts, grants, cooperative agreements, and cooperative research and development agreements ("CRADAs").

We believe these authorities, which are among those exercised by the Department of Health and Human Services (HHS) and its Biomedical Advance Research and Development Authority (BARDA) for the purpose of encouraging the development of medical countermeasures, are readily applicable to unmet needs in the area of antimicrobials.

(4) Expand tropical disease priority review vouchers, as established under FDAAA, to apply to qualified infectious disease products.

Section 1102 of the FDAAA authorizes FDA to award priority review vouchers to sponsors of certain tropical disease product applications; a priority review is a review conducted with a goal date of 6 months. A priority review voucher may be used by the sponsor who obtains it, or may be transferred from the sponsor (including by sale) to another sponsor of a human drug application. This policy is intended to create a positive, 'tradeable' incentive to encourage companies to pursue drug development in neglected global diseases and could be easily expanded to the development of priority antimicrobials.

(5) Create infectious disease product development grants modeled on FDA's successful orphan product development (OPD) grants.

Like the 7-years of market exclusivity authorized under the Orphan Drug Act, orphan development grants administered by FDA successfully encourage the clinical development of products for use in rare diseases or conditions. Congress could authorize grants modeled on this successful program 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.

(6) Codify the task force on global antimicrobial resistance.

In November 2009, the EU and the U.S. agreed to establish a transatlantic task force to address antibiotic resistance. Under the U.S./EU agreement, the Task Force will focus on appropriate therapeutic use of antimicrobial drugs in the medical and veterinary communities, prevention of both healthcare- and community-associated drug-resistant infections, and strategies for improving the pipeline of new antimicrobial drugs. Congress should codify the task force and expand its focus beyond transatlantic antimicrobial resistance. The task force could expand upon, or complement, the current federal Interagency Task Force on Antimicrobial Resistance.

(7) Improved access to home infusion antibiotic treatment especially in the Medicare program.

Medicare is the one health care program that fails to cover home infusion services in the traditional fee-for-service – or Part B – arena. All other major health insurers as well as Medicare Advantage plans provide coverage for antibiotics infused in the home setting. Home infusion coverage would allow patients in need of antibiotic treatment -- including those with MRSA or other resistant bacterial infections to receive the drugs they need at home in a non-hospital setting. Not only is home-based care easier for the patient, but keeping these patients out of the hospital would help reduce the spread of such resistant infections in acute care setting.

I'd like to thank Congressman Engel for his leadership in seeking to include in the recently enacted health care reform law changes to Medicare that would provide for home infusion services. While this change was not included in the law as enacted, this lack of

Medicare coverage and other reimbursement challenges remain part of the larger equation of incentives that must be addressed in order to draw more companies, researchers, and investors into this space.

Conclusion

Mr. Chairman, 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 act on the consensus recommendations that I, and many others, have offered as steps towards assuring the development of the next generations of first-line drugs to combat resistant infections, as well as managing the emergence, transmission, and treatment of drug resistant organisms.

Endnotes

[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.
[4] L.L. Maragakis and T.M. Perl, Acinetobacter baumannii: *Epidemiology, Antimicrobial Resistance, and Treatment Options*, Clinical Infectious Diseases, 2008;46:1254-1263.
[5] K.M. Hujer, et. al, *Analysis of Antibiotic Resistance Genes in Multidrug-Resistant Acinetobacter sp. Isolates from Military and Civilian Patients Treated at the Walter Reed Army Medical Center*, Antimicrobial Agents and Chemotherapy, 2006; 50 (12): 4114-4123.
[6] J. Chong, *A mysterious adversary preys on the war's wounded; A strange, drug-resistant bacterium was infecting troops. Few had heard of it, and no one was sure of its origin*, Los Angeles Times, Sept 30, 2007, A1.
[7] K. Kaye et al., *The Deadly Toll of Invasive Methicillin-Resistant* Staphylococcus aureus *Infection in Community Hospitals*, Clinical Infectious Diseases, 2008;46:1568-1577.
[8] 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.
[9] *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.
[10] *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.
[11] 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.
[12] A Coming Storm: Prevention of a Public Health Catastrophe, Cubist Pharmaceuticals, 2010.