EXHIBIT Z

TO DECLARATION OF
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MICROBIAL THREATS TO HEALTH

EMERGENCE, DETECTION, AND RESPONSE

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Committee on Emerging Microbial Threats to Health
in the 21st Century

Board on Global Health

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termined to be the appropriate drug in this situation, and an ample supply was readily available. The same may not be true when the next influenza pandemic eventually occurs, likely resulting in tens of thousands of deaths. Although stockpiling of antiviral drugs for influenza is a component of the pandemic plan developed by the United States and WHO (WHO, 1999e), we have yet to begin stockpiling antivirals effective against influenza. The time has come to move forward with this plan and determine which drugs are needed; the quantity required; the costs of production, storage, and distribution; and the authority under which the drugs will be used.

> **The U.S. Secretary of Health and Human Services and the U.S. Secretary of Homeland Security should protect our national security by ensuring the stockpiling and distribution of antibiotics, antivirals (e.g., for influenza), and antitoxins for naturally occurring or intentionally introduced microbial threats.** *The federal government should explore innovative mechanisms, such as cooperative agreements between government and industry or consortia of government, industry, and academia, to accelerate these efforts.*

INAPPROPRIATE USE OF ANTIMICROBIALS

For a variety of reasons previously discussed, the pharmaceutical industry is developing fewer new antimicrobials than in previous years. Whereas it appeared at one time that an endless supply of effective new drugs to treat resistant infections would exist, such is no longer the case. Therefore, immediate action must be taken to preserve the effectiveness of available drugs.

Factors leading to the increasing problem of antimicrobial resistance are well known and understood. Many genes for resistance occur on cassettes that can move between organisms, across species boundaries (Leverstein-van Hall et al., 2002), and between chromosomes and plasmids. Resistance genes in bacteria are commonly grouped together on the same mobile genetic elements, with the crucial practical consequence that the use of any single drug may select for resistance to a wide group of drugs. Thus, an antimicrobial employed in food and animal production that has never before been used to treat infection in humans can select for resistance to other drugs used to treat humans.

Resistant bacteria often persist in vivo even in the absence of continued selection by antibiotics, although in some cases resistance gradually diminishes once antibiotic pressures have been reduced. One explanation for continued resistance involves the lethal effect of the loss of certain plasmids when bacteria divide. Some resistant microbes are less fit, but resistant strains arising in a clinical context are generally virulent and can often persist for extended periods of time once established. Therefore, it is imperative to actively pursue and address the problem; it will be too late to effect useful change once most microbes have become resistant to the available drugs.

Antibiotic resistance resulting from the inappropriate overuse of antibiotics is not a new problem. A number of expert committees and professional organizations have studied the problem, issued reports, and made recommendations (Alliance for the Prudent Use of Antibiotics, 2001; CDC, 2001o; FDA, 2000; GAO, 1999; Center for Science in the Public Interest, 1998; NRC, 1999). Unfortunately, little has been done to change the situation, especially in the United States. Resistance due to the inappropriate use of antibiotics compromises the efficacy of many classic and highly effective antibiotics, such as penicillin for pneumococci and vancomycin for enterococci, as well as that of some newer antibiotics, such as ciprofloxacin and other types of fluorinated quinolones for gonococci, *Salmonella*, and *Campylobacter*. The recent discovery of an enterococcal gene for vancomycin resistance in *S. aureus* was alarming even though it had been predicted on the basis of the ability of the genes to transfer across species boundaries during mixed culture (CDC, 2002d). In the case of enterococcal and staphylococcal infection, alternative therapies have been introduced, but resistance to these new drugs has already been documented (Tsiodras et al., 2001; Herrero et al., 2002). The specter of untreatable infections—a regression to the pre-antibiotic era—is looming just around the corner.

Preventing the overuse of antimicrobials is not an easy task because of the revolutionary effects the drugs have had on human and animal health. Because antimicrobials are highly effective, there is an understandable tendency to use them in any situation in which they might be helpful. These effective drugs are relatively inexpensive compared with other medical interventions. Patients demand the drugs when they have an illness they imagine to be treatable with antibiotics. Doctors prescribe antibiotics for that same reason, often in the absence of diagnostic tests to determine the etiology of infection, and also because patients want and expect to be treated with them. In many areas of the world where little money is available for health care, antimicrobials are readily available without a doctor's prescription, and as a result are often taken unnecessarily or inadequately. Many problems associated with antimicrobial resistance have arisen in poor and developing areas of the world, and have subsequently spread globally.

In addition to avoiding the inappropriate use of antibiotics to treat viral disease, prudence dictates use of the appropriate antimicrobial when an etiologic diagnosis is made. For example, the rapid rise in drug-resistant malaria has led to the development of newer, generally more expensive therapies for the disease. This in turn has resulted in an increase in the prescribing of these newer drugs, even in areas where there is no demonstrated resistance to first-line therapies. The use of first-line therapies must be continued in areas where resistance has not been documented, and newer therapies should be used only when first-line therapies are ineffective or in areas of resistance. To this end, it is essential to monitor resistance patterns around the world.

Decreasing Inappropriate Use of Antimicrobials in Human Medicine

Decreasing the inappropriate use of antimicrobials in human medicine is a complex task that requires a multipronged effort fueled by a sense of urgency. The inappropriate use of antibiotics for treatment of viral diseases can be averted by the increased use of available diagnostic tests and the development of better point-of-care, inexpensive, rapid, sensitive, and specific diagnostic tests, which would enable the rational use of new antivirals as they become available (see the earlier discussion of the development of diagnostics). The decreased use of antibacterials for viral respiratory infections and other syndromes should lessen selective pressures for the emergence of resistant bacteria. FDA has recently included this message on label inserts of antibiotics.

If this important objective is to be achieved, the general public and health care providers must be better educated and informed about the importance of administering antimicrobial therapy properly. The need is urgent to both educate and monitor all categories of practitioners and drug dispensers in developing countries where medicines are sold directly to the public over the counter and dispensed by private practitioners in an ad hoc manner. More attention needs to be given to improving practitioner education and compliance. Patient care would be improved by the development and dissemination of better evidence-based treatment guidelines. More research is needed on methods for treating infections to minimize the emergence of resistance without a loss of efficacy. Infection control programs must be supported in hospitals in an effort to decrease the transmission of resistance both within the hospitals and in the community. Surveillance for patterns of resistance in hospitals and in the community must be continued and expanded; this will require a coordinated effort among public health organizations, private medicine, and industry. Because resistant microbes arise throughout the world and travel broadly to all regions, the needs and problems of the economically and health care disadvantaged regions of the world must be considered.

The world is facing an imminent crisis in the control of infectious diseases as the result of a gradual but steady increase in the resistance of a number of microbial agents to available therapeutic drugs. Although defining the precise public health risk of emergent antimicrobial resistance is not a simple task, there is no doubt that the problem is of global concern and is creating dilemmas for the treatment of infections in both hospitals and community health care settings.

CDC, FDA, professional health organizations, academia, health care delivery systems, and industry should expand efforts to decrease the inappropriate use of antimicrobials in human medicine through (1) expanded outreach and better education of health care providers, drug dispensers, and the general public on the inherent dangers associated with the inappropriate use of antimicrobials, and (2) the increased use of diagnostic tests, as well as the development and use of rapid diagnostic tests, to determine the etiology of infection and thereby ensure the more appropriate use of antimicrobials.

Decreasing Inappropriate Overuse of Antimicrobials in Animal Husbandry and Agriculture

Clearly, a decrease in the inappropriate use of antimicrobials in human medicine alone is not enough. Substantial efforts must be made to decrease inappropriate overuse of antimicrobials in animals and agriculture as well.

Although estimates vary widely, the total amount of antimicrobials used in Europe and the United States in animal husbandry and agriculture far outweighs the total used in humans (McEwen and Fedorka-Cray, 2002). The majority of this use is for growth promotion or preventive therapy in healthy animals. Mounting evidence suggests a relationship between antimicrobial use in animal husbandry and an increase in bacterial resistance in humans (Alliance for the Prudent Use of Antibiotics, 2002), a view supported by an IOM committee that reviewed the use of drugs in food animals (IOM, 1999b). The use of antimicrobials in food animals leads to antibiotic resistance, which can then be transmitted to humans through the food supply (Swartz, 2002; Fey et al., 2000; Smith et al., 2002; White et al., 2001).

A study published in 2001 found that 20 percent of ground meat samples obtained from supermarkets in the Washington, D.C., metropolitan area were contaminated with *Salmonella*. Of these bacteria, 84 percent were resistant to at least one antibiotic and 53 percent to at least three antibiotics (White et al., 2001). This study supports previous findings that foods of animal origin are potential sources of ceftriaxone-resistant *Salmonella* infections in humans. Similarly, researchers found that between 17 and 87 percent of chickens obtained in supermarkets in four states contained strains of *Enterococcus faecium* that were resistant to quinupristin–

dalfopristin, an approved antimicrobial for use in humans (McDonald et al., 2001). The researchers believed that the use of virginiamycin, an antibiotic of the streptogramin group, in farm animals had created a reservoir of streptogramin–resistant *E. faecium* in the food supply, which could contribute to foodborne dissemination of resistance as the clinical use of quinupristin–dalfopristin increases.

Substantial evidence supports that certain types of resistant organisms, such as vancomycin-resistant enterococci, emerged initially in animals because of the use of similar drugs for growth promotion or prophylaxis (O'Brien, 2002). Consideration of this association led to a ban on the use of avoparacin, a vancomycin analogue, in Europe (Wegener et al., 1999). The decreased use of antimicrobials for growth promotion or prophylaxis in many European countries has been associated with a subsequent stabilization in resistance or a gradually decreasing resistance in animal flora (Aarestrup et al., 2001). WHO has called for all antimicrobials used for disease control in food animals to be prescribed by veterinary health care providers, and for termination or rapid phase-out of antimicrobials used for growth promotion if they are used for human treatment (WHO, 2000f). Various other groups have suggested that because of the increasing risk of antimicrobial resistance, the subtherapeutic use of antibiotics for growth promotion should be banned (some would include use for prophylaxis in the ban as well) if they are also used in humans (Union of Concerned Scientists, 2002; Alliance for the Prudent Use of Antimicrobials, 2002).

The main argument against a ban is the potential economic hardships to livestock and poultry producers, which would result in higher costs for consumers. According to the IOM Committee on the Use of Drugs in Food Animals, such a ban would increase the price of meat by an estimated 0.013 to 0.06 cents per pound; this translates to $4.84 to $9.72 per person each year, depending on the meat and the cut (IOM, 1999b). Yet, evidence suggests that animals can be raised efficiently without the use of growth-promoting antimicrobials (Emborg et al., 2001; Wierup, 2001).

Critics of the ban also argue that it would result in poorer production efficiency and an increased incidence of infectious disease in animals. However, it has been noted that subtherapeutic antibiotics are most effective in animals under the stress of inadequate nutrition and suboptimal sanitary conditions (Braude et al., 1953); therefore, improved hygiene and changes in animal husbandry practices to control disease could potentially eliminate the need for growth promoters (Emborg et al., 2001). In Denmark, the elimination of antimicrobial growth promoters from broiler chicken feed did not result in a change in death rates or a decrease in kilograms of broilers produced per square meter. Danish scientists also reported that the decreased use of virginiamycin and avilamycin in animals was followed by decreases in resistance to these drugs (Aarestrup et al., 2001).

FDA should ban the use of antimicrobials for growth promotion in animals if those classes of antimicrobials are also used in humans.

The committee endorses the Public Health Action Plan to Combat Antimicrobial Resistance developed by the Interagency Task Force on Antimicrobial Resistance and the recommendations of the WHO Global Strategy for the Containment of Antimicrobial Resistance (see Boxes 4-9 and 4-10). Although the broad scope of these recommendations defies easy implementation, we must seize the opportunity immediately to do as much as we can while organizing the resources and plans needed to carry out other initiatives. To do nothing is, in effect, to allow the continued evolution of antimicrobial-resistant microbes, which poses serious near- and long-term threats to global health. The total burden of human illness due to resistant bacteria that have been transferred from animals to humans is unknown, but the guiding principle should be that we must do what the available evidence suggests will help stem the tide of increasing resistance before it is too late. By endorsing these recommendations, we will join belatedly much of the rest of the developed world, which already has made similar recommendations and, in many cases, implemented them. These changes should be accompanied by substantial outcomes research on the effects on animal health, resistance prevalence in animals and humans, and the economics of food production.

VECTOR-BORNE AND ZOONOTIC DISEASE CONTROL

The majority of emerging infectious diseases are zoonoses (i.e., diseases transmitted from animals to humans under natural conditions). Vector-borne and rodent-borne diseases are especially notable in this regard, remaining major causes of morbidity and mortality in humans in the tropical world and representing a large proportion of newly emerged diseases (see the discussion in Chapter 3). Exacerbating the situation is the potential for many of these agents to be weaponized and used by bioterrorists. Because of their resurging public health importance and their exceptional ability to cause epidemics, vector-borne and zoonotic diseases will undoubtedly continue to pose significant risks to human health in the future.

Unfortunately, the national and international capacity to address these diseases is limited. The many reasons for this include (1) the lack of efficacious vaccines for many of these pathogens; (2) decreased support for and deterioration of the public health surveillance and control infrastructure for vector-borne and zoonotic diseases; (3) erosion in the numbers of scientists trained in relevant fields, including medical entomology, vector ecology, zoonoses, and tropical medicine; (4) the development of resistance to drugs

BOX 4-9
WHO Global Strategy for Antimicrobial Resistance

In response to the growing problem of antibiotic resistance, WHO has worked with many partners, including the American Society for Microbiology and the Alliance for the Prudent Use of Antibiotic (APUA), to develop the WHO Global Strategy for Containment for Antimicrobial Resistance. The seven key recommendations emanating from the 25 expert reports used to formulate the strategy are summarized below.

Increase Awareness of the Antibiotic Resistance Problem

International organizations:
- Obtain worldwide commitments to establish prudent antibiotic use policies

National and municipal organizations:
- Publicize the outcomes of programs from other countries
- Educate the general public
- Promote communication
- Evaluate the curricula of universities

Health care institutions:
- Use effective teaching methods for education prescribers

Health care workers:
- Educate the general public

Improve Surveillance of Antibiotic Resistance

National and municipal organizations:
- Coordinate local surveillance networks
- Recruit leaders for surveillance networks
- Support a reference laboratory
- Share results of surveillance with international organizations
- Monitor resistance in food animals
- Monitor sentinel human populations

Health care institutions:
- Develop local surveillance network
- Maintain a laboratory with adequate quality assurance and trained technicians

Health care workers:
- Initiate a local surveillance network

Pharmaceutical companies:
- Undertake postmarking surveillance to detect the emergence of resistance to new antibiotics
- Support surveillance networks

Improve Antibiotic Use in People

National and municipal organizations:
- Enforce the prudent use of antibiotics
- Create national and regional guidelines
- Update guidelines based on surveillance data
- Eliminate financial incentives that promote the misuse of antibiotics
- Monitor advertising
- Consider the impact of new drugs on resistance during the drug approval process
- Limit general access to new drugs
- Establish postmarking surveillance accords

Health care institutions:
- Establish an Infection Control Committee
- Establish a Drugs and Therapeutics Committee
- Establish guidelines for appropriate antibiotic use
- Appoint an antimicrobial resistance monitor
- Reduce the spread of infection
- Create pharmacy reports

- Establish and disseminate list of essential drugs
- Educate employees
- Maintain a laboratory

Health care workers:
- Prescribe antibiotics prudently
- Improve hygiene

Improve Antibiotic Use in Animals

National and municipal organizations:
- Increase awareness of the antibiotic resistance problem
- Regulate antibiotic prescriptions for animals
- Restrict growth promoter use in animals
- Regulate antibiotic use in animals
- Set a risk standard for resistance
- Consider human and nonhuman uses simultaneously
- Monitor advertising

Veterinarians:
- Promote a prudent use of antibiotics in animals
- Develop local guidelines for antibiotic use

Food animal producers:
- Improve farm hygiene
- Reduce the use of antibiotics as growth promoters
- Improve animal husbandry

Researchers:
- Perform risk–benefit analysis of growth promoter use
- Assess environmental impact
- Examine food processing and distribution methods

Encourage New Product Development

National and municipal organizations:
- Provide incentives to industry
- Protect intellectual property rights
- Facilitate networking

Pharmaceutical companies:
- Increase research and development in several areas

Increase Resources to Curb Antibiotic Resistance in the Developing World

International organizations:
- Share results of surveillance internationally
- Secure technical and financial support for developing countries
- Invest in a worldwide vaccine strategy to reduce antibiotics
- Ensure the availability of vaccines and quality drugs
- Facilitate communication among the countries of the world
- Safeguard privacy and human rights
- Promote appropriate international laws

National and municipal organizations:
- Decrease the risk of infectious disease
- Ensure antibiotic availability
- Share resources with other countries

Increase Funding for Surveillance, Research, and Education

National and municipal organizations:
- Increase funding for a surveillance network
- Increase funding for research
- Increase funding for education

SOURCE: World Health Organization, 2001i.