EXHIBIT T

TO DECLARATION OF
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FDA Website (Battle of the Bugs)

U.S. Department of Health & Human Services

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Drugs

Battle of the Bugs: Fighting Antibiotic Resistance

Ever since antibiotics became widely available about 50 years ago, they have been hailed as miracle drugs--magic bullets able to destroy disease-causing bacteria.

But with each passing decade, bacteria that resist not only single, but multiple, antibiotics--making some diseases particularly har to control--have become increasingly widespread. In fact, according to the Centers for Disease Control and Prevention (CDC), virtually all significant bacterial infections in the world are becoming resistant to the antibiotic treatment of choice. For some of us bacterial resistance could mean more visits to the doctor, a lengthier illness, and possibly more toxic drugs. For others, it could mean death. The CDC estimates that, each year, nearly 2 million people in the United States acquire an infection while in a hospital, resulting in 90,000 deaths. More than 70 percent of the bacteria that cause these infections are resistant to at least one of the antibiotics commonly used to treat them.

Antibiotic resistance, also known as antimicrobial resistance, is not a new phenomenon. Just a few years after the first antibiotic, penicillin, became widely used in the late 1940s, penicillin-resistant infections emerged that were caused by the bacterium Staphylococcus aureus (S. aureus). These "staph" infections range from urinary tract infections to bacterial pneumonia. Methicillin, one of the strongest in the arsenal of drugs to treat staph infections, is no longer effective against some strains of S. aureus. Vancomycin, which is the most lethal drug against these resistant pathogens, may be in danger of losing its effectiveness; recently some strains of S. aureus that are resistant to vancomycin have been reported.

Although resistant bacteria have been around a long time, the scenario today is different from even just 10 years ago, says Stuart Levy, M.D., president of the Alliance for the Prudent Use of Antibiotics. "The number of bacteria resistant to many different antibiotics has increased, in many cases, tenfold or more. Even new drugs that have been approved are confronting resistance, fortunately in small amounts, but we have to be careful how they're used. If used for extended periods of time, they too risk becoming ineffective early on."

How Resistance Occurs

Bacteria, which are organisms so small that they are not visible to the naked eye, live all around us--in drinking water, food, soil, plants, animals, and in humans. Most bacteria do not harm us, and some are even useful because they can help us digest food. Bu many bacteria are capable of causing severe infections.

The ability of antibiotics to stop an infection depends on killing or halting the growth of harmful bacteria. But some bacteria resist the effects of drugs and multiply and spread.

Some bacteria have developed resistance to antibiotics naturally, long before the development of commercial antibiotics. After testing bacteria found in an arctic glacier and estimated to be over 2,000 years old, scientists found several of them to be resistan against some antibiotics, most likely indicating naturally occurring resistance.

If they are not naturally resistant, bacteria can become resistant to drugs in a number of ways. They may develop resistance to certain drugs spontaneously through mutation. Mutations are changes that occur in the genetic material, or DNA, of the bacteria. These changes allow the bacteria to fight or inactivate the antibiotic.

Bacteria also can acquire resistant genes through exchanging genes with other bacteria. "Think of it as bacterial sex," says David White, Ph.D., a microbiologist in the Food and Drug Administration's Center for Veterinary Medicine. "It's a simple form of mating that allows bacteria to transfer genetic material." The bacteria reproduce rapidly, allowing resistant traits to quickly spread to futur generations of bacteria. "The bacteria don't care what other bacteria they're giving their genes to," says White. This means that resistance can spread from one species of bacteria to other species, enabling them to develop multiple resistance to different classes of antibiotics.

Combating Resistance

In 1999, 10 federal agencies and departments, led by the Department of Health and Human Services, formed a task force to tackle the problem of antimicrobial resistance. Co-chaired by the CDC, the FDA, and the National Institutes of Health, the task force issued a plan of action in 2001. Task force agencies continue to accomplish the activities set forth in the plan. The success of the plan--known as the Public Health Action Plan to Combat Antimicrobial Resistance--depends on the cooperation of many entities, such as state and local health agencies, universities, professional societies, pharmaceutical companies, health care professionals, agricultural producers, and the public.

All of these groups must work together if the antibiotic resistance problem is to be remedied, says Mark Goldberger, M.D., director of the FDA office responsible for reviewing antibiotic drugs. "This is a very serious problem. We need to do two things: facilitate th development of new antimicrobial therapy while at the same time preserve the usefulness of current and new drugs."

Preserving Antibiotics' Usefulness

Two main types of germs--bacteria and viruses--cause most infections, according to the CDC. But while antibiotics can kill bacteria, they do not work against viruses--and it is viruses that cause colds, the flu, and most sore throats. In fact, only 15 percent of sore throats are caused by the bacterium Streptococcus pyogenes, which results in strep throat. In addition, viruses cause most sinus infections, coughs, and bronchitis. And fluid in the middle ear, a common occurrence in children, does not usually warrant treatment with antibiotics unless there are other symptoms.

Nevertheless, "Every year, tens of millions of prescriptions for antibiotics are written to treat viral illnesses for which these antibiotics offer no benefits," says David Bell, M.D., the CDC's antimicrobial resistance coordinator. According to the CDC, antibiotic prescribing in outpatient settings could be reduced by more than 30 percent without adversely affecting patient health.

Reasons cited by doctors for overprescribing antibiotics include diagnostic uncertainty, time pressure on physicians, and patient demand. Physicians are pressured by patients to prescribe antibiotics, says Bell. "People don't want to miss work, or they have a sick child who kept the whole family up all night, and they're willing to try anything that might work." It may be easier for the physician pressed for time to write a prescription for an antibiotic than it is to explain why it might be better not to use one.

But by taking an antibiotic, a person may be doubly harmed, according to Bell. First, it offers no benefit for viral infections, and second, it increases the chance of a drug-resistant infection appearing at a later time.

"Antibiotic resistance is not just a problem for doctors and scientists," says Bell. "Everybody needs to help deal with this. An important way that people can help directly is to understand that common illnesses like colds and the flu do not benefit from antibiotics and to not request them to treat these illnesses."

Following the prescription exactly is also important, says Bell. People should not skip doses or stop taking an antibiotic as soon as they feel better; they should complete the full course of the medication. Otherwise, the drug may not kill all the infectious bacteria allowing the remaining bacteria to possibly become resistant.

While some antibiotics must be taken for 10 days or more, others are FDA-approved for a shorter course of treatment. Some can be taken for as few as three days. "I would prefer the short course to the long course," says Levy. "Reservoirs of antibiotic resistance are not being stimulated as much. The shorter the course, theoretically, the less chance you'll have resistance emerging, and it gives susceptible strains a better chance to come back."

Another concern to some health experts is the escalating use of antibacterial soaps, detergents, lotions, and other household items. "There has never been evidence that they have a public health benefit," says Levy. "Good soap and water is sufficient in most cases." Antibacterial products should be reserved for the hospital setting, for sick people coming home from the hospital, and for those with compromised immune systems, says Levy.

To decrease both demand and overprescribing, the FDA and the CDC have launched antibiotic resistance campaigns aimed at health care professionals and the public. A nationwide ad campaign developed by the FDA's Center for Drug Evaluation and Research emphasizes to health care professionals the prudent use of antibiotics and offers them an educational brochure to distribute to patients.

The FDA published a final rule in February 2003 that requires specific language on human antibiotic labels to encourage doctors to prescribe them only when truly necessary. The rule also requires a statement in the labeling encouraging doctors to counsel their patients about the proper use of these drugs.

Stimulating Drug Development

The FDA is working to encourage the development of new antibiotics and new classes of antibiotics and other antimicrobials. "We would like to make it attractive for the development of new antibiotics, but we'd like people to use them less and only in the presence of bacterial infection," says Goldberger. This presents a challenge, he says. "Decreased use may result in sales going down, and drug companies may feel there are better places to put their resources."

Through such incentives as exclusivity rights, the FDA hopes to stimulate new antimicrobial drug development. Exclusivity protects a manufacturer's drug from generic drug competition for a specific length of time.

The FDA has a variety of existing regulatory tools to help developers of antimicrobial drugs. One of these is an accelerated approval process for drugs that treat severely debilitating or life-threatening diseases and for drugs that show meaningful benefit over existing prescription drugs to cure a disease.

The FDA is also investigating other approaches for speeding the antimicrobial approval process. One approach is to reduce the size of the clinical trial program. "We need to streamline the review process without compromising safety and effectiveness," says Goldberger. "One of the things that we are trying to look at now is how we can substitute quality for quantity in clinical studies." It has been difficult to test drugs for resistance in people, says Goldberger. "Although these resistant organisms are a problem, they are still not so common that it is very easy to accumulate patients."

Research

Scientists and health professionals are generally in agreement that a way to decrease antibiotic resistance is through more cautious use of antibiotic drugs and through monitoring outbreaks of drug-resistant infections.

But research is also critical to help understand the various mechanisms that pathogens use to evade drugs. Understanding these mechanisms is important for the design of effective new drugs.

The FDA's National Center for Toxicological Research (NCTR) is studying the mechanisms of resistance to antibiotic agents among

bacteria from the human gastrointestinal tract, which can cause serious infections.

In addition, the NCTR has studied the amount of antibiotic residues that people consume in food from food-producing animals and the effects of these residues on human intestinal bacteria. This information led to a new approach for assessing the safety of antibiotic drug residues in people, which may be adopted by the FDA to help review drugs for food animals.

To find out more about the broad range of issues associated with antimicrobial resistance, see the FDA's Web site at Combating Antibiotic Resistance [1], and the CDC's Web site at www.cdc.gov/drugresistance/ [2]

Upper Respiratory Infections and Antibiotics

Most upper respiratory infections are usually caused by viruses--germs that are not killed by antibiotics. Talk with your doctor abou ways to feel better when you are sick. Ask what you should look for at home that might mean you are developing another infection for which antibiotics might be appropriate.

Illness	Antibiotic usually needed?
Cold	No
Flu	No
Chest Cold (in otherwise healthy children and adults)	No
Sore Throats (except strep)	No
Bronchitis (in otherwise healthy children and adults)	No
Runny Nose (with green or yellow mucus)	No
Fluid in the Middle Ear (otitis media with effusion)	No

CDC

Fluid in the Middle Ear

Fluid in the middle ear, also called otitis media with effusion, is a common condition in children. Fluid often accumulates in the ear, just like in the nose, when a child has a cold. In the absence of other symptoms, fluid in the middle ear usually doesn't bother children, and it almost always goes away on its own without treatment, says Janice Soreth, M.D., director of the FDA's Division of Anti-Infective Drug Products. "It usually does not need to be treated with antibiotics unless it is accompanied by additional signs o symptoms or it lasts a couple of months."

If your doctor does not prescribe an antibiotic for your child, do not insist on one. Taking an antibiotic when it is not necessary can be harmful. It increases the risk of getting an infection later that antibiotics cannot kill.

Instead, "observe your child," says Soreth. "If symptoms change, call your doctor to seek further help." Symptoms to watch for include fever, irritability, decreased appetite, trouble sleeping, tugging on the ear, or complaints of pain. "If symptoms occur, it doesn't mean the doctor misdiagnosed the condition," says Soreth. "What started out as a viral condition may have morphed into a bacterial infection several days later. If this happens, an antibiotic may be appropriate."

What You Can Do to Help Curb Antibiotic Resistance

Don't demand an antibiotic when your health care provider determines one isn't appropriate. Ask about ways to help relieve your symptoms.

Never take an antibiotic for a viral infection such as a cold, a cough, or the flu.

Take medicine exactly as your health care provider prescribes. If he or she prescribes an antibiotic, take it until it is gone, even if you're feeling better.

Don't take leftover antibiotics or antibiotics prescribed for someone else. These antibiotics may not be appropriate for your current symptoms. Taking the wrong medicine could delay getting correct treatment and allow bacteria to multiply.

Links on this page:

1. /ForConsumers/ConsumerUpdates/ucm092810.htm
2. http://www.cdc.gov/drugresistance/