Testimony of John H Powers, MD
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Good morning. My name is John Powers. I was a physician-scientist at the US Food and Drug Administration for the last 8 years, the last 5 of which I was the Lead Medical Officer for Antimicrobial Development and Resistance Initiatives. I would like to state that I do not consider myself as having "blown a whistle", since I pointed out the very issues that I will discuss today to FDA managers up the chain of command. I chose to leave the agency to pursue other research opportunities after over half a decade of attempting to advance the science of clinical trials in infectious diseases, feeling that I could better serve the public outside the agency. There are numerous individuals in both FDA and the drug industry who work hard appropriately evaluating new medicines for people. I learned a tremendous amount at FDA and I would still be there today if I felt I could perform my job in the way it should be done.

Many of the recent discussions regarding evaluation of new drugs have focused on their safety. However, there are also important issues with the evaluation of effectiveness, especially regarding antibiotics. In 1962, the Food, Drug and Cosmetic Act was amended to state there must be substantial evidence of effectiveness from adequate and well-controlled trials in order to justify the adverse events inherent with the use of all drugs. In the absence of evidence of effectiveness, any adverse effect, no matter how rare, is not justifiable.

The drug Ketek is a symptom of much larger problem. Over the last 25 years, FDA has approved approximately 68 new drug applications for ear infections in children, sinus infections and bronchial infections in patients with underlying lung disease. All of

these drugs were approved based on so-called "noninferiority" trials. While the word "noninferior" strictly means "not worse", the purpose of these trials is in fact to rule out an amount by which the new drug's effectiveness may be *worse* than an old drug. Therefore, noninferiority trials are really "not too much worse" trials. Showing a new drug is potentially worse than an old drug when the effectiveness of the old drug is unclear is like the Billy Preston song, "nothing from nothing leaves nothing". An evaluation of previous placebo controlled trials shows that 12 of 17 studies in sinusitis and 9 of 14 studies in bronchial infections lack evidence of a benefit for antibiotics and the situation is similar for ear infections. Based on these data, showing that Ketek may be less effective than older drugs does not provide evidence that Ketek is effective at all in sinus and bronchial infections, and this was clear at the time the drug was approved in 2004. Initiation of a noninferiority trial with Ketek in ear infections in children is inappropriate and unethical, as it exposes children to harm without the potential to clearly provide evidence of benefits.

Noninferiority trials are justifiable in serious infections where the benefits of antibiotics are large and reproducible. However, even in serious diseases the trial must be designed, performed and analyzed appropriately in order to provide meaningful results. The major problem is that many of the common safeguards in clinical trials that protect us from drawing false conclusions are less useful in noninferiority trials. For instance, if one performs a trial to evaluate a drug in patients with pneumonia, but most of the patients enrolled in the trial have the common cold, it is much easier to make two drugs appear similar when in fact this says nothing about the new drug's effectiveness in pneumonia. This is like testing a new parachute against an older proven parachute, when

all the test subjects are jumping out a plane that is standing still and only two inches off the ground. Everyone will do well, but it says nothing about how the new parachute will really work in a real life situation.

Lack of effectiveness is an even larger problem with antibiotics than it is for other types of drugs. If a non-antibiotic doesn't work, it only affects the person who takes it. If an antibiotic doesn't work, it affects not only the person who takes it, but can also affect other people who don't take it by spreading resistance not only to that drug but to other related drugs as well. Antimicrobial resistance *is* a safety issue as lack of effectiveness can promote the very problem of antibiotic resistance we are trying to combat.

We need new antibiotics to combat the inevitable increase in antibiotic resistance, but approval of ineffective and therefore inherently unsafe antibiotics is not an incentive for drug development. After approval of numerous antibiotics whose effectiveness is unclear, we have seen no boom in antibiotic development, and in fact drug sponsors have exited this field. Developing appropriate economic incentives to promote development are the province of Congress, not the FDA.

We need to address these problems now. FDA needs to require sponsors to perform superiority trials in self-resolving diseases. Even in serious diseases, FDA needs to require appropriately designed, conducted and analyzed noninferiority trials to give clinicians the information they need to make decisions for their patients. FDA needs to address the issue of drugs that still carry approvals for self-resolving diseases without evidence of effectiveness. FDA needs to promptly publish new guidances based on

appropriate scientific and regulatory principles and remove the old guidances from their website now, since they continue to mislead drug sponsors.

The bottom line is this is about people, not about "bad bugs". Most of us in this room have taken antibiotics or will need to take them. We must preserve this precious resource that has been one of the marvels of modern medicine by ensuring these drugs are effective, safe, and used appropriately. Thank you.