**Testimony Before the FDA Anti-infective Diseases Advisory Board**
**October 17, 2013**

I'm Lisa Plymate, and I come before you to speak as a clinician and a member of the National Physicians Alliance. I have no conflicts of interest. I have been practicing internal medicine in Washington state for over 30 years. I came here today from Seattle because it is crucial to me that information on which I make practice decisions be based on unbiased, rigorous science that includes meaningful human trials.

When I see a patient with an infection, my two primary sources of data are my patient and the culture results, which identify the pathogen and advise which antibiotics should lead to meaningful clinical outcomes – in terms of symptomatic improvement, ability to resume usual function and survival. For a clinician, accurate, scientifically-valid reports of antibiotic sensitivity are crucial.

The briefing before us today deals with adjusting breakpoints for minimal inhibitory concentrations, which get interpreted as sensitivities for us on our lab reports. It is the FDA's responsibility from the time of drug approval to set and adjust susceptibility criteria. I rely on the FDA to serve as our "court of last resort" in using unbiased, scientific standards to make its decisions. However, outside groups like the Clinical and Laboratory Standards Institute (CLSI) have suggested they be allowed to make changes to susceptibility criteria, as you see before you today. My first concern is for a potential **conflict-of-interest** here. I have concerns that CLSI allows pharmaceutical companies to join as members – for fees of up to $25,000 annually - and includes drug company employees on its committees. Companies that produce and market antibiotics should not be involved in setting or adjusting MIC breakpoints. Simply disclosing conflicts of interest is insufficient to prevent bias.

My second main concern is that of **methodology**. Experimental data obtained *in vitro* or in animals is invaluable, and pharmacokinetic/pharmacodynamic modeling is useful to generate hypotheses, but these must be validated in people. As an example, in 2010, CLSI suggested lowering the breakpoints for ceftriaxone. Tamma et al (1) at Johns Hopkins reviewed outcomes in 136 cases of Enterobacter sepsis admitted over the preceding decade whose organisms would not have been considered sensitive by the new criteria. They found that with the CSLI suggestions, there would have been a 300% increase in isolates that would no longer have been considered susceptible to ceftriaxone, but that this shift of breakpoints would "not have affected important clinical outcomes, including mortality and microbiologic failure." The authors conclude that "although *in vitro* data are an important first step in guiding antibiotic use in patients, we believe they are in need of confirmation from clinical outcomes data as MIC changes can significantly impact patient care." This was a simple, retrospective review that should have been done before recommendations to make changes were made.

Antibiotics are societal drugs. Lowering breakpoints in this manner would lead clinicians like myself to prescribe newer, more broad-spectrum antibiotics in direct conflict with our need to conserve existing agents. This could be detrimental to patients, increasing their risk of secondary infections (such as *Clostridia difficile*) and to our community, contributing to escalating antibiotic resistance and healthcare costs. I do not want my choices shifted because someone working for a drug company decides to alter the definition of sensitivities on my lab report unless there is hard clinical data to support such a change.

So in the proposals before you, I ask you to consider first, is there clinical evidence that changing sensitivity breakpoints will help patients in meaningful ways, or might changes simply lead clinicians to select newer, more expensive antibiotics that might be less effective or more toxic? My patients are not test tubes. They are not immune-deficient, leukopenic mice, nor can their responses to medications always be predicted by Monte Carlo simulations. Our reference standard has to be what happens in people. And throughout the decision process, in determining which cutoffs we use to decide which antibiotics are most likely to be effective for each individual, we have to trust that the science being done is conflict-of-interest free.

Respectfully submitted, Lisa Plymate, MD, Seattle, WA

1Tamma PD, Wu H, Gerber JS, Hsu AJ, Tekle T, Carrol KC and Cosgrove SE. Outcomes of children with Enterobacteriaceae bacteremia with reduced susceptibility to ceftriaxone: do the revised breakpoints translate to improved patient outcomes? Ped Inf Dis J 2013 Sep PMID: 23470679