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IDSA
Infectious Diseases Society of America

November 17, 2009

The Honorable Rosa DeLauro
Chair, Appropriations Subcommittee on
House Agriculture, Rural Development,
Food and Drug Administration,
and Related Agencies
U.S. House of Representatives
Rayburn House Office Building
Washington DC 20515

Dear Chairwoman DeLauro:

The Infectious Diseases Society of America (IDSA), comprised of more than 9,000 infectious diseases physicians and scientists, wishes to raise several important concerns about your November 11th letter to Dr. Peggy Hamburg, Commissioner, U.S. Food and Drug Administration (FDA), in which you call on the Agency to stop plans to "outsource" antibiotic efficacy testing. The content of your letter to Commissioner Hamburg suggests that you may only have received partial [and/or biased] background information that resulted in a misunderstanding of both the issues and the scientific complexities related to the development of antibacterial drug susceptibility testing "breakpoints," which guide physicians in their daily treatment of sick patients. It should be stated upfront that you, the FDA, IDSA, and patient advocates all have the same goal in mind—the protection of patients' safety and health. Unfortunately, the complexity of this particular issue and the difficulty in understanding its underpinnings has caused some individuals to adopt and promote approaches that are not supported by the facts. Of critical importance and in direct response to what you have heard, the FDA does not plan to "outsource" the essential function of deciding on antibacterial breakpoint values. Rather, the Agency would maintain its statutory authority, carefully review information collected from both laboratory and clinical sources that is collected by qualified professional nationally or internationally recognized standard setting organizations regarding breakpoint recommendations under consideration, and then decide either to accept or not accept the breakpoint recommendations. Finally, it is unfortunate that you have received inaccurate information about the nature of evidence available to support updates to breakpoints. Let us take each of these points in turn.

It appears that you have received partial [and/or biased] background information.

To put these issues in context, a bit of history is needed. Antibiotic susceptibility testing in the United States was developed and has been performed according to guidelines of the Clinical and Laboratory Standards Institute (CLSI) and its institutional predecessor, the National Committee on Clinical Laboratory Standards (NCCLS), for approximately 40 years. *CLSI's methods and their associated interpretations are recognized around the world as state-of-the-art.*

Inspection agencies and organizations such as the College of American Pathologists (CAP) and the Joint Commission on the Accreditation of Healthcare Organizations (JCAHO) judge clinical laboratories in part on how well they adhere to CLSI methods. Likewise, regulatory documents and guidelines from the FDA recommend that pharmaceutical companies use CLSI methods in developing susceptibility tests for new antibacterial drugs.

Breakpoints actually comprise three distinct elements: A testing method, quality control procedures, and interpretive guidelines for the results. Over the years, FDA has always used information submitted by drug sponsors in their new drug applications to define these three elements at the time an antibacterial drug is approved. But, FDA has not had the capacity to continually revise and update these elements as improved methods are identified and as antibacterial drug resistance has developed over the course of the approved product's life cycle, including after antibiotics have gone off patent protection. This difficulty has been magnified as many of these drugs have been marketed only in generic form.

The only organization in the United States capable of and devoted to this task has been CLSI which, as your letter acknowledges, is a volunteer, consensus standards setting organization whose work is highly regarded. The members of the CLSI Subcommittee on Antimicrobial Susceptibility Testing are infectious diseases physicians, clinical microbiologists, and pharmacologists from academia and the professions, government (including FDA and the Centers for Disease Control and Prevention (CDC)), and industry. As a group, these individuals are the thought leaders in the field and are highly respected by their peers.

CLSI uses an open, consensus process to permit it to evaluate and validate emerging information. By having all relevant parties at the table, the CLSI consensus process ensures that all relevant data are available and considered. As a consequence, we view the inclusion in this process of individuals representing the professions, government, and industry as a strength rather than a weakness.

CLSI regularly updates guidance on susceptibility testing methods and interpretive breakpoints, with revisions being based on new scientific knowledge about emerging resistance to antibacterial agents. **Thus, CLSI's collected methods and guidance on interpretation encapsulates the totality of 40 years of insights and as such is an asset that cannot readily be duplicated.**

Prior to 2006-07, the FDA Center for Devices and Radiological Health (CDRH) guidance allowed antimicrobial susceptibility device manufacturers (85-90% of laboratories in the US use these automated devices) to include in their device algorithms both FDA-established breakpoints listed in package inserts at the time of the drug's approval as well as the more up-to-date CLSI breakpoints. However, there was no specific process ensuring that microbiology data were updated across all drug labels and device algorithms in a consistent way. Beginning with the FDA Amendments Act of 2007, the Agency now is required to periodically ensure that microbiology information in product labels is reviewed and updated. IDSA lobbied Congress for inclusion of such a requirement for regular updates and is pleased that Congress took this important action.

In considering how best to address the problem of out-of-date microbiology information in product labels, FDA has realized that the work required to appropriately and promptly perform this task is enormous. Given that summaries developed by an organization such as CLSI over many years represent the state-of-the-art and cannot readily be duplicated, the FDA has proposed that reference to standards developed by nationally and internationally recognized standard setting organizations such as CLSI could be used to support the agency's efforts.

It appears that you have received misinformation about the way in which the agency proposes to proceed.

The approach proposed by the Agency does not represent "outsourcing" an essential function. Rather, the Agency retains final authority, but intends to access the carefully considered scientific data developed through a transparent, unbiased consensus body consisting of the best scientists and physicians in the field. *The FDA will maintain its statutory authority: It will select the elements of the reference standard that it believes are valid by reviewing the methods and updated breakpoint recommendations. Final authority will rest in all cases with the agency.*

As a practical matter, given CLSI's existence, expertise, and respected position among infectious diseases physicians and other stakeholders, we believe it would be a waste of taxpayers' monies to ask FDA to try to replicate this process internally. Moreover, we are not sure that, even given the necessary resources, the Agency could create a process equal to CLSI's given the clinical expertise required, which currently does not exist nor likely ever could exist within the Agency.

Further, an FDA effort to redevelop all the information internally would require years — years during which patients would be increasingly at risk due to lack of updated information. As infectious diseases physicians, our primary concern is patient care and safety as related to the diagnosis and treatment of infectious diseases. Accordingly, it is imperative that physicians receive clinically relevant and reliable antimicrobial susceptibility test results upon which to base their treatment decisions. Any further delay in implementing updates based on state-of-the-art information such as that developed by CLSI is unacceptable to us and to our patients.

It appears that you have received inaccurate information about the nature of the evidence available to support updates to breakpoints.

Finally, we think it is important to correct an important error of fact in your letter to Commissioner Hamburg relating to the manner in which antibacterial drug susceptibility breakpoints are developed by both FDA and CLSI. Your letter states that "FDA decisions about antibiotic resistance and efficacy of drugs already on the market should be based on data from outcomes of clinical studies in humans, not the kinds of test tube studies or animal studies that CLSI primarily relies upon to make its determinations". Both FDA and CLSI consider *in vitro* (test tube) data, pharmacokinetic and pharmacodynamic (achievable drug levels and drug behavior based on both human and animal model studies) data, and data from human clinical trials in their development of susceptibility breakpoints. This information is extensively reviewed and validated at the time of new drug approval.

However, when resistance develops over time to marketed antibacterial drugs, there are no new formal human clinical trials upon which to base decisions as there are for new drugs. For reasons that will be discussed below, formal comparative prospective therapy studies to validate resistance are not possible. Nevertheless, physicians must have regularly updated guidance on how to use these drugs even when optimal data do not exist.

Unfortunately, the individuals who have been advising you on this point appear to have unrealistic expectations regarding implementation in the real world. In the real world setting, the experts who volunteer their time and expertise to the CLSI consensus process use the existing data—in vitro microbiologic studies, in vivo animal studies, pharmacologic information, and the available clinical information (e.g., reports of clinical failures of treatment in humans)—to revise susceptibility breakpoints on a regular basis so that patients will be treated appropriately and safely.

Unfortunately, formal comparative studies to validate resistance are not possible. Indeed, conducting such trials when there is an expectation of resistance to the antibiotic being studied would be unethical. Further, such studies would run slowly and leave patients at risk for years longer than necessary. To elaborate on these thoughts, breakpoints may require revision when only a small minority of organisms has developed resistance. To find and study only patients infected with such organisms is surprisingly difficult — the information needed to prove infection with a resistant isolate is usually not available until several days after trial enrollment. Moreover, we would not want to wait through the several years required for such a study to change breakpoints that we know are grossly incorrect. Finally, such studies would be unethical. At the simplest level, such studies would require patients infected with resistant bacteria to be deliberately given therapy judged inadequate based on other information. In this context, it is important to remember that resistant bacteria can (and are) studied regularly in the test tube and in animal models that mimic human infection. When it is clear both that a drug cannot kill a bacterium in a test tube and that the drug cannot cure an infected animal, it is then equally clear from extensive experience that placing a patient at risk by using such inadequate therapy is unethical and inappropriate.

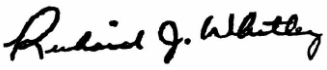
As physicians, we deal with uncertainties such as these each and every day in our attempt to treat serious infections and save lives. We recognize the imperfections in our process, but we also recognize that access to accurate breakpoint information helps to reduce some of this uncertainty. This is why updating breakpoints on a regular basis is so important, and this is the service that, currently in the United States, only CLSI provides.

Our request.

Accordingly, IDSA respectfully requests that you agree to support the Agency's plan to review the annually updated breakpoints published by CLSI or other appropriate nationally or internationally recognized standard setting bodies, keeping in mind that the agency will then determine whether to sanction these recommendations based upon the best available scientific and clinical evidence. This approach is in the best interest of patient care and safety, represents sound judgment, and does not represent "outsourcing" of FDA's decision-making authority.

IDSA stands ready and willing to work with you and other members of Congress to ensure that FDA accesses, in the most expeditious manner possible, the best available information to update susceptibility breakpoints both now and in the future. Please contact Robert J. Guidos, JD, IDSA's vice president for public policy and government relations, at rguidos@idsociety.org or by phone at 703-299-0202 if you have questions.

Sincerely,



Richard Whitley, MD, FIDSA
President

cc: Margaret Hamburg, MD, Commissioner, FDA
Kevin Brennan, Chief of Staff, Office of Chairwoman Rosa DeLauro