August 23, 2006

Division of Dockets Management
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Room 1061
Rockville, Maryland 20852

CITIZEN PETITION

The undersigned organization submits this petition to request amendment by the Center for Drug Evaluation and Research (CDER) of the vancomycin HCl package insert to reflect modifications of the antimicrobial susceptibility interpretive criteria to better recognize emerging resistance resulting in compromised patient outcomes. The Clinical and Laboratory Standards Institute (CLSI, formerly the National Committee for Clinical Laboratory Standards [NCCLS]) has established a pre-eminent role in consensus standardization of test procedures, quality control, and interpretive criteria for antimicrobial susceptibility testing. CLSI is recognized for the application of its inclusive, open, and transparent voluntary consensus process to laboratory and other healthcare issues. CLSI is recognized globally for its responsiveness to emerging trends in patterns of resistance to antimicrobial agents.

A. ACTION REQUESTED

This Petition requests that the Commissioner direct CDER to amend the package insert of the antibiotic vancomycin to include newly revised susceptibility interpretive criteria that recognize emerging resistance to this agent in the important bacterial pathogen *Staphylococcus aureus*. **Specifically, it is requested that the minimal inhibitory concentration indicative of susceptibility to vancomycin be lowered from 4 µg/mL or less to 2 µg/mL or less. It is proposed that the intermediate category range be lowered from 8 to 16 µg/mL to 4 to 8 µg/mL. Finally, it is recommended that the resistance category definition be lowered from 32 µg/mL or greater to 16 µg/mL or greater**. These changes to the susceptibility interpretive criteria will better take into account the emerging lower-level resistance to vancomycin that has resulted in delayed responses to vancomycin therapy in severely ill patients or therapeutic failures associated with use of the drug to treat infections due to *S. aureus* strains with vancomycin MICs of 4 µg/mL or greater.

B. STATEMENT OF GROUNDS

The following analysis of microbiological, pharmacokinetic, and clinical data, when taken as a whole, suggests that a change in the vancomycin susceptibility interpretive criteria for *S. aureus* is necessary. These data have been extracted from the published medical literature with the exception of some of the clinical outcomes data for a subset of patients presented in Table 1.

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Background and Clinical Significance

Vancomycin is an important parenteral antibiotic that has been in clinical use for more than 40 years. It has been useful for treating serious infections due to gram-positive bacteria in patients who are penicillin-allergic, and during the past three decades it has been the mainstay for therapy of serious infections due to methicillin-resistant *Staphylococcus aureus* (MRSA) in the United States and many other countries. Acquired resistance to vancomycin did not emerge until the late 1980s, when it was found in *Enterococcus* spp., not in staphylococci. Those first vancomycin-resistant enterococci possessed a plasmid-encoded five-gene operon that could be transferred to other enterococci and to *S. aureus* during *in vitro* mating experiments (1,2,3). It was widely held that the *vanA* operon would eventually be transferred in nature to *S. aureus*, most probably to MRSA. Such an event would severely compromise therapy of serious MRSA infections, if the resistance factors were widely spread among MRSA strains (4). Indeed, high-level vancomycin resistance in MRSA was first recognized in a patient in Michigan in 2002 (5). The vancomycin MIC of that isolate was 1024 µg/mL, and the *vanA* gene cluster was resident on a plasmid very likely obtained by transfer *in situ* to an MRSA strain from a vancomycin-resistant *Enterococcus faecalis* that was coinfecting the same wound of the patient. While some speculated that this was an isolated event that would likely not be repeated, a second vancomycin-resistant *S. aureus* (VRSA) isolate was reported just a few months later in Pennsylvania (6). That strain contained a modified *vanA* operon, and demonstrated a lower vancomycin MIC (32 µg/mL), but was still considered resistant. The lower MIC of the Pennsylvania VRSA strain was likely due to the instability of the large plasmid that harbored the *vanA* gene (7). Since then, there have been four additional VRSA strains reported, with MICs ranging from 32 to 512 µg/mL (8,9, CDC unpublished data). Prior to the emergence of vancomycin resistance in enterococci and in MRSA, the FDA and CLSI (then NCCLS) had defined susceptibility criteria for vancomycin as an MIC of 4 µg/mL or less as susceptible, MICs of 8 to 16 as being intermediate, and MICs of 32 µg/mL as indicative of resistance. These definitions had been established before any strains with acquired vancomycin resistance were available for study.

In advance of the first recognition of high-level vancomycin resistance in MRSA, *S. aureus* strains had been reported with lower-level vancomycin resistance. The first of such strains was described by Hiramatsu and colleagues in Japan (10). While they reported their strains with vancomycin MICs of 8 or 16 µg/mL as vancomycin "resistant" because of the poor clinical response in patients who had been treated with vancomycin, these organisms were subsequently described as vancomycin intermediate *S. aureus* or VISA strains, based upon the interpretive breakpoints employed in the United States at that time as described above. These strains did not contain the *vanA* gene cluster, but instead possessed an unusually thickened cell wall that contained numerous dipeptides capable of binding vancomycin and impeding its penetration to the site of vancomycin activity, which is the cell membrane where the cell wall precursors are assembled. The VISA strains also had several metabolic and structural changes that differed from normal, wild-type strains of *S. aureus* (10,11,12). Thereafter, similar VISA strains with vancomycin MICs of 8 to 16 µg/mL were reported in the United States, as well as several

other countries (13,14,15,16,17,18). While these strains could be detected by the standard CLSI/NCCLS reference broth microdilution method and by growth on the vancomycin screening agar developed for detection of VRE, they were not detected reliably by disk diffusion or by some commercial susceptibility testing devices (19).

A second group of *S. aureus* strains, also described by Hiramatsu and coworkers, demonstrated a lower level of vancomycin resistance that was expressed in a heterogeneous manner (10). These strains contained subpopulations of no more than 1 in 10^5 to 1 in 10^6 colony forming units (CFUs) with vancomycin MICs of 8 to 16 μg/mL, where the majority of cells appeared to be vancomycin susceptible (MICs of 1 to 4 μg/mL) by standard MIC testing methods. The first such strain (designated Mu3) was isolated from a patient with persistent staphylococcal pneumonia (18). The apparent clinical failure of vancomycin is what led the Japanese investigators to examine the strain's vancomycin susceptibility profile more closely. The Japanese investigators utilized complex population analysis studies that could separate the "homogeneously" vancomycin resistant (or using CLSI categories, intermediate or VISA) strains from the heterogeneous ones, later called hVISA for heteroresistant-VISA or hetero-VISA. Initially, opinions differed among knowledgeable microbiologists and infectious disease experts regarding the clinical significance of heterogeneously resistant strains in light of the fact that the vancomycin MICs of such strains were $\leq$ 4 μg/mL using standard CLSI testing methodology. It was particularly difficult to collect clinical outcomes data when only very cumbersome microbiology techniques were available to recognize the hVISA strains. Despite this, the Japanese and British literature described these strains as hetero-vancomycin-resistant *S. aureus* (VRSA) based upon the definitions in those countries that vancomycin resistance was represented by an MIC $\geq$ 8 μg/mL, and presence of cells within the hVRSA/hVISA population that expressed MICs of that magnitude. Further strengthening the link between the VISA and hVISA strains has been the finding that both often have mutations in the structural or regulatory genes associated with the accessory gene regulator (*agr*) pathway. These mutations result in decreased production of virulence factors and toxins, increased production of biofilm matrix, and render them "tolerant" to the killing action of vancomycin (20,21,22). These changes may lead to further genetic alterations that result in increases in cell wall thickness and elevated MICs of vancomycin and also daptomycin (23,24,25). Thus, *S. aureus* has evolved over the past 40 years and has adapted in some cases to the prolonged exposure to vancomycin.

While clinical outcomes data on patients infected with VISA or hVISA strains have been hard to assemble because of difficulties in accurately identifying such strains in routine clinical microbiology laboratories, some data have emerged. Fridkin et al of the Centers for Disease Control and Prevention (CDC) reported a study of 19 infections caused by *S. aureus* isolates that showed reduced susceptibility to vancomycin (designated as SA-RSV) (26). The vancomycin MIC for four isolates was 8 μg/mL; the MIC of the remaining 15 isolates was 4 μg/mL. Forty-two control cases (MRSA infections for which the vancomycin MICs of the isolates were $\leq$ 2 μg/mL) were also assessed. All cases regardless of whether the vancomycin MICs of the isolates were 4 or 8 μg/mL had similarly poor outcomes. The attributable mortality of the SA-RSV infections was 63% compared with 12% for the MRSA controls. Risk factors for being a

case were exposure to vancomycin and having an MRSA infection in the past two to three months. Predictors of in-hospital death were bacteremia and SA-RSV infection. Thus, patients with SA-RSV (hVISA) infections (MICs of 4 μg/mL) had similar outcomes to those with VISA infections (MICs of 8 μg/mL).

Charles et al from Australia reviewed the clinical data for all 46 MRSA bacteremia cases that occurred in their hospital during a one-year period (27). The MRSA isolates recovered from the bacteremic patients were tested blindly by a population analysis method to identify hVISA and VISA isolates. There were no VISA isolates identified, but there were five hVISA isolates. The chart reviews of the five hVISA cases indicated that those patients had sustained fever and bacteremia, had high inoculum density infections, and had inappropriately low vancomycin trough serum levels early in the course of their therapy (which may have selected the more resistant hVISA portion of the population of cells). A second Australian study reported by Howden et al reviewed the records of 25 patients in which hVISA infections were confirmed by culture and population analysis (28). The vancomycin MICs for the isolates ranged from 2 to 4 μg/mL based upon standard testing methods. Of the 25 cases, 19 failed vancomycin therapy (i.e., bacteremia persisted for >7 days or had a positive sterile site culture after 21 days of therapy with a glycopeptide). PFGE strain typing demonstrated multiple patterns among the isolates ruling out the spread of a single strain in the hospital. Four of the patients died. Of the 21 patients treated with regimens other than vancomycin, 16 were cured (mostly with linezolid).

A United States study conducted by Sakoulas et al indicated that as vancomycin MICs of MRSA isolates reached ≥ 2 μg/mL, the number of clinical failures for patients treated with vancomycin increased (29). The isolates from patients that failed vancomycin therapy typically showed bactericidal activity of < 99.99% kill versus a killing rate of >7.1 logs for isolates from patients who responded favorably to vancomycin therapy. Moise-Broder et al reported the results of a study of 63 evaluable patients with serious MRSA infections that failed or were intolerant of vancomycin therapy (30). As the vancomycin MICs of the isolates increased from 0.5 to 2 μg/mL, the rate of therapeutic failures increased, even though all the isolates were classified as vancomycin-susceptible by standard test methods.

Finally, Table 1 below comprised of a small subset of published and unpublished cases of invasive MRSA infections due to strains with vancomycin MICs of 4 μg/mL has been compiled to highlight the overall poor outcomes of these patients, especially the failure of vancomycin to clear the patients' persistent bacteremias.

Table 1. Clinical Failures of Vancomycin in Patients Infected With *S. aureus* for Which the Vancomycin MICs for Vancomycin Were 4 µg/mL						
Patient	Age/Sex	Source of Infection	Organism	Vancomycin MIC	Evidence for Failure	Reference
1	80 M	Endocarditis	MRSA	4	+BC 29 days on Vanco	28
2	73 F	Endocarditis	MRSA	4	+BC 8 days on Vanco	28
3	66 F	Endocarditis	MRSA	4	+BC 13 days on Vanco	28
4	45 M	Bacteremia	MRSA	4	+BC 12 days on Vanco	28
5	63 M	Bacteremia	MRSA	4	+BC 33 days on Vanco	28
6	83 M	Bacteremia	MRSA	4	+BC 8 days on Vanco	28
7	Not defined	Bacteremia	MRSA	4	+BC >7 days on Vanco	27
8	Not defined	Bacteremia	MRSA	4	+BC 12 days on Vanco	Kohner P et al, Abstract #116 ASM 2002
9	59 M	Infected dialysis catheter, bacteremia	MRSA	4	+BC 39 days on vanco	Nolte F, unpublished data
10	60 M	Endocarditis	MRSA	4	+BC 42 days on vanco	Weinstein M, unpublished data
11	81 M	PVE	MRSA	4	+BC 22 days on Vanco	Gold H, Weil G, et al, RCM unpublished data
12	57 F	Vertebral osteomyelitis/ bacteremia	MSSA	4	+BC after >10 weeks on Vanco	S Pillai, unpublished data
13	45 F	Endocarditis	MSSA	4	+BC 35 days on Vanco	Zervos M, Abstract #P1457 ECCMID 2006
14	44 M	Infected TIPS	MRSA	4	+BC 42 days on Vanco	Lewis JS, unpublished data

Animal Model Data

Limited studies using the rabbit endocarditis model have suggested that the increased subpopulation MICs of hVISA strains represented a cause of vancomycin treatment failure (31).

The Establishment and Reassessment of Susceptibility Breakpoints by CLSI

The Clinical and Laboratory Standards Institute (formerly NCCLS) has worked continuously since the formation of the first susceptibility testing subcommittee in 1968 to provide performance standards for antimicrobial susceptibility testing for use by clinical microbiology laboratories. Over the years, the Subcommittee on Antimicrobial Susceptibility Testing has worked to refine the process of establishing interpretive criteria or "breakpoints" for both quantitative broth and agar dilution tests that give rise to minimal inhibitory concentration (MIC) values that must be interpreted for clinical application (32). These interpretive criteria are used by almost every clinical microbiology laboratory in the U.S., and by many laboratories in Canada, Latin America, Europe, Australia, Asia, and Africa. The American National Standards Institute (ANSI) has accredited the CLSI susceptibility testing standards as U.S. National Standards. During this 34-year period, CLSI has earned the reputation as the world's leading organization in setting antimicrobial susceptibility testing breakpoints.

The CLSI Subcommittee on Antimicrobial Susceptibility Testing (AST) reviews an extensive amount of microbiology, pharmacology, and clinical therapy data in establishing or revising breakpoints. The data review is outlined in detail in CLSI/NCCLS document M23-A2—*Development of* In Vitro *Susceptibility Testing Criteria and Quality Control Parameters; Approved Guideline—Second Edition*, 2001 (33). The document describes the types of data used for defining breakpoints, including:

- Microbiology data, including MICs for wild-type organisms within the spectrum of activity and intended use of the antimicrobial agent and MICs of strains that contain well-recognized resistance mechanisms that affect the drug class.

- Pharmacokinetic and pharmacodynamic data, including levels of the drug in various body fluids and tissues of normal volunteers and in patients. Also included are determinations of serum protein binding and serum half-life determinations. These values are integrated with knowledge of how the drug class is known to kill microorganisms, i.e., concentration-dependent or time-dependent killing in order to arrive at values that compare the peak drug levels to MICs, the area under the drug concentration curve (AUC), and the time above MIC in the body fluid.

- Clinical response data, including clinical and microbiological response data that relate drug MICs with successes or failures of treatment as determined during the clinical trials leading up to submission of the New Drug Application to the FDA.

Unlike the FDA, however, CLSI continuously reviews clinical data published in the peer-reviewed literature that describes clinical response data for a drug with specific organisms that may reflect emerging resistance to the drug under assessment. In this way, CLSI is uniquely positioned to revise interpretive breakpoints when significant new mechanisms of resistance emerge after the initial FDA approval of a drug and its widespread clinical use. Examples of emerging resistance that have prompted action by CLSI to revise earlier breakpoints include extended-spectrum cephalosporin resistance in *Streptococcus pneumoniae*, fluoroquinolone resistance in *S. pneumoniae*, and vancomycin resistance in *Enterococcus* spp.

The Decision by CLSI to Lower the Vancomycin Breakpoints

In January 2004, the CLSI AST Subcommittee began consideration of a proposal by CDC representatives to modify the minimal inhibitory concentration (MIC) interpretive criteria (i.e., breakpoints) for vancomycin testing of *S. aureus*. Data regarding the failure of vancomycin to cure *S. aureus* infections when the vancomycin MICs of the organisms were in the intermediate (8 to 16 μg/mL) or borderline susceptible (4 μg/mL) range suggested that the susceptible breakpoint used for MIC testing needed to be reconsidered. Over a two-year period, the subcommittee reviewed data from a variety of sources including: 1) *in vitro* susceptibility testing data from the United States and Europe; 2) data on vancomycin heteroresistance in *S. aureus* isolates (i.e., VISA and hVISA); 3) limited pharmacokinetic and pharmacodynamic data from studies in mice; 4) published clinical data on the efficacy of vancomycin for treating *S. aureus* infections, including results of recent clinical trials of vancomycin versus linezolid for treatment of pneumonia; and 5) results of an Emerging Infections Network survey on treatment of persistent methicillin-resistant *S. aureus* (MRSA) bacteremia. Several of the infectious disease clinicians serving as members and advisors of the AST Subcommittee also presented their published and unpublished clinical experiences with using vancomycin to treat borderline vancomycin-susceptible MRSA infections. After considering all of the data presented at four meetings over the two-year period, the subcommittee voted to lower the vancomycin breakpoint to: **≤ 2 μg/mL, susceptible; 4 to 8 μg/mL, intermediate; ≥ 16 μg/mL, resistant.** The purpose of the change in breakpoints was to provide greater patient safety by identifying those strains of *S. aureus* that may be predicted to respond poorly to vancomycin therapy in serious infections. Identifying such strains would also facilitate healthcare system epidemiology efforts to prevent cross-transmission of strains with reduced susceptibility to vancomycin. A review of several data sets indicated that lowering the breakpoints as described would not encroach on the normal, wild-type population of *S. aureus* and overestimate resistance. Surveillance studies demonstrated that the modal vancomycin MIC for *S. aureus* was typically 1 μg/mL (34,35,36) and that isolates for which the MICs are 4 μg/mL were rare. The Surveillance Network (TSN) data from United States laboratories confirmed that vancomycin MICs of 4 μg/mL were rare (<1%) among over 240,000 *S. aureus* isolates. Data from Europe made available via the European Union Committee on Antimicrobial Susceptibility Testing (EUCAST) website

[http://217.70.33.99/Eucast2/SearchController/regShow.jsp?Id=1214] showed no *S. aureus* isolates with vancomycin MICs of 4 μg/mL among almost 85,000 isolates. Therefore, the new CLSI vancomycin breakpoints were felt to increase the margin of patient safety when using a potentially toxic antibiotic for therapy of serious *S. aureus* (usually MRSA) infections without reducing the number of normal, wild-type strains defined as susceptible to the drug. The new vancomycin breakpoints for *S. aureus* were published in January 2006 in CLSI document M100-S16 (32).

Barriers to Implementing the New CLSI Breakpoints for Vancomycin

With few exceptions, the interpretive criteria included in the CLSI standards and their supplements are identical to those included in the FDA-approved drug labels. However, in a few instances, the CLSI interpretive criteria differ from those of the approved drug label, often due to the emergence of resistance to the drug that has been recognized since the drug label was initially approved and that has resulted in a change in the CLSI breakpoints. CLSI has as part of its mission the development of test methods and interpretive criteria that assist in the recognition of emerging antimicrobial resistance. *The FDA Guidance Document (Class II Special Controls Guidance Document: Antimicrobial Susceptibility Test [AST] Systems; Guidance for Industry and FDA*, February 5, 2003) for submission of requests for premarket (510[k]) clearance states that "Agreement of interpretive results (SIR) between a new device under evaluation and an NCCLS standard reference method. FDA interpretive criteria should be used but the NCCLS criteria, if different, may also be applied if based on more current recommendations for detecting organism resistance when resistant mechanisms were not recognized (or did not exist) during the FDA drug evaluation." This guidance document supplements the general controls of the Federal Food, Drug, and Cosmetic Act premarket notification requirements described in 21 CFR 807 Subpart E. Until recently, the CDRH reviewed submissions for 510(k) device clearance that included an assessment of device performance using the current CLSI interpretive criteria, as well as the FDA drug label criteria in those few instances where differences exist. However, as of late, the CDRH has contended that device labels and interpretive breakpoints must match the CDER-approved drug label explicitly. This effectively prevents U.S. clinical microbiology laboratories from implementing the newest CLSI susceptibility testing recommendations aimed in some cases at detecting emerging antimicrobial resistance, which is contrary to the ideal of maximizing patient safety.

Specifically, this petition asks that:

CDER revise the approved drug label for vancomycin to include the new vancomycin interpretive criteria of $\leq$ 2 μg/mL, susceptible; 4 to 8 μg/mL, intermediate; $\geq$ 16 μg/mL, resistant for *S. aureus*. This would make it possible for clinical microbiology laboratories to report results of *S. aureus* tests that include detection of strains with elevated MICs that may lead to clinical failures.

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C. ENVIRONMENTAL IMPACT

The requested relief does not require an environmental assessment or environmental impact statement under 21 CFR § 25.31.

D. ECONOMIC IMPACT

As provided in 21 CFR 10.30(b), economic impact information is to be submitted only when requested by the Commissioner following review of the petition.

The undersigned certifies that, to the best of their knowledge and belief, this petition includes all information known to the petitioner that is unfavorable to the petition.

Sincerely,

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