American Cleaning Institute  
Attention: Paul C. DeLeo  
Associate Vice President, Environmental Safety  
1331 L Street, NW, Suite 650  
Washington, DC 20005

Dear Mr. DeLeo:

Please refer to your March 21, 2016 submission to docket FDA-2015-N-0101-1295 (Safety and Effectiveness for Health Care Antiseptics; Topical Antimicrobial Drug Products for Over-the-Counter Human Use) which contained a draft in vitro efficacy protocol titled: "Determination of the Minimum Inhibitory Concentration (MIC) and Minimum Bactericidal Concentration (MBC) of Six Test Materials".

Our review is complete and we have the following comments:

As proposed in the 1994 TFM We continue to believe that a GRAE determination for a health care antiseptic active ingredient should be supported by adequate in vitro characterization (testing against 25 fresh clinical isolates and 25 laboratory strains) of the antimicrobial broad spectrum activity of the ingredient.

You also noted that there was a precedent of the agency accepting a reduced MIC/MBC data set in the approval of NDAs for topical antiseptic products. For example, this was the case for Avagard Health Care Personnel Hand Antiseptic (NDA 021074) and Chloraprep Patient Preoperative and Preinjection Skin Preparation (NDA 021555). In both cases, the agency accepted only MIC data from 5 of the 25 ATCC strains and 5 of 25 fresh clinical isolates for a total of 10 strains for each of 21 microorganisms. You stated that you believe a similar approach would be appropriate for any of the health care antiseptic active ingredients which are currently part of the health care antiseptic monograph for which new in vitro test data is deemed necessary by the agency. In addition, you stated that your approach have the added benefit that you would provide the more relevant MBC data along with the MIC data.

At the time of approval of Avagard and Chloraprep, we had evaluated numerous chlorhexidine gluconate drug product applications evaluating a broad spectrum of antimicrobial activity through MICs. Therefore, we no longer recommend MIC testing against the organisms described in the 1994 TFM for chlorhexidine gluconate products because we have sufficient information regarding the spectrum of antimicrobial activity.
As such, MIC testing is not necessary to support approval for chlorhexidine gluconate drug products. Instead, we recommend a modified in vitro time-kill study.

In contrast, we currently do not have a complete in vitro (MIC or MBC) assessment for the following active ingredients: ethyl alcohol, isopropyl alcohol, benzalkonium chloride, benzethonium chloride, chloroxylenol, and povidone-iodine. Therefore, we highly encourage you to conduct the in vitro MICs or MBCs as described in the 2015 Proposed Rule for Health Care Antiseptics (80 FR 25166 at 25177) in order to fulfill the effectiveness data gap for the active ingredients. Based on comments provided to the docket, we are currently re-evaluating the criteria for final formulation testing.

Additionally:

1. Increase the number of laboratory ATCC strains and clinical isolates to comply with the 2015 Proposed Rule for Health Care Antiseptics (80 FR 25166 at 25177) in order to fulfill the effectiveness data gap for the active ingredients.

2. If the test strain was lyophilized or from cryogenic stock cultures, subculture the strain three times before using the assay to ensure that the organisms have reached optimal growth and metabolic status.

3. Include one antibiotic resistant microorganism *Staphylococcus aureus* MRSA (ATCC 33591 or 33592) to be tested for the neutralization validation testing.

4. Include the name of the neutralizer used in the study when you submit your final report.

5. Include the following controls for the neutralization validation study: neutralizer effectiveness testing, neutralizer toxicity testing, test organism viability control testing, and test material control testing.


7. Evaluate the microbial recovery population on average of the three replicate platings.
If you have any questions, call Celia Peacock, Regulatory Project Manager at (301) 796-4154.

Sincerely,

Theresa Michele, MD
Director
Division of Nonprescription Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research