January 15, 2010

Joan Harrigan-Farrelly  
Director, Antimicrobials Division  
Office of Pesticide Programs  
U.S. Environmental Protection Agency  
Washington, DC 20460

Dear Ms. Harrigan-Farrelly:

On behalf of the Society for Healthcare Epidemiology of America (SHEA), the Association for Professionals in Infection Control and Epidemiology (APIC) and the American Society for Healthcare Environmental Services (ASHES), we thank you for the opportunity to provide responses to your questions regarding infection reduction claims. We fully support your goal of ensuring that antimicrobial agents have no unreasonable effects on humans or the environment and are pleased to provide input to facilitate your decision-making process.

We believe the enclosed responses outline the top-line criteria and concerns that would need to be addressed in considering EPA’s proposal to approve quantitative infection reduction label claims. Having thoroughly considered the complexities raised by some of the related issues, our organizations would welcome an opportunity to meet with EPA representatives to discuss these important issues in a more informal forum. It is difficult to adequately address all pertinent scenarios and information in writing without being unduly verbose. We further believe that such a meeting would improve general healthcare and end-user confidence in the review and registration process.

Again, thank you for the opportunity to provide responses to your questions. SHEA, APIC and ASHES hope to have the opportunity to meet with you to further discuss these issues.

Sincerely,

Neil Fishman  
Christine Nutty, RN  
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Enclosures
EPA Questions: Infection Reduction Label Claims

1. Are infection reduction claims, quantitative and/or qualitative, appropriate for disinfectant products?

Based on current laboratory testing registrants submit to the Antimicrobials Division, Office of Pesticide Programs U.S. Environmental Protection Agency for registration, we believe the answer is no. However we propose the following criteria and associated scientific evidence as a roadmap towards quantitative infection reduction claims only. Given what we have outlined as suggested criteria, we do not think qualitative claims can be considered.

Quantitative infection reduction label claims would be appropriate as long as certain criteria are met by the applicant seeking registration. The EPA should develop the criteria with the assistance of representatives from the appropriate professional organizations such as SHEA, APIC, IDSA, ASM and ASHES. This could be accomplished by convening a healthcare-oriented panel to address the unique issues raised by these questions and others arising during the crafting of this response. The panel could be modeled after or affiliated with the EPA Scientific Advisory Panel on Antimicrobial Research Strategies for Disinfectants. Recommended criteria could include the following:

a. Appropriate studies (e.g., a randomized controlled trial; cross-over design) demonstrate a clinically meaningful reduction in infections.

b. The decreased rate of infections that should be clinically and statistically meaningful. Of importance, the rate reduction findings in these studies need to identify the relative contribution of the disinfectant compared to all other variables, including the Hawthorne effect. The vast majority of literature in the field of healthcare epidemiology/infection prevention involves interventions around an outbreak or cluster of infections caused by a particular pathogen. Numerous interventions are typically implemented simultaneously making conclusions of relative contribution of each individual element very difficult. One of the goals of studies submitted by registrants should be a clear, unambiguous assessment of the attributable impact the product played in the reduction in infection rates.

c. Potential confounding variables must be identified and their possible impact on the findings addressed.

d. Products must be safe (non-hazardous to humans and animals, and that resistance to the antimicrobial product is unlikely).

e. At least two appropriate clinical, independent trials should be conducted with well-described goals, methods, outcomes, and statistics, demonstrating statistically significant efficacy and accepted or published in appropriate peer-reviewed literature.

f. The label claim should be restricted to the appropriate setting and population in which the efficacy is demonstrated. For example, if the product has an infection reduction claim in the acute care setting it would not necessarily be given an infection reduction claim in the home health or non-acute care setting. Similarly, if the claim appeared to have efficacy for a specific subpopulation in an acute-care setting, this restriction would also apply and need to be noted.

g. An infection reduction claim against specific disease-causing microorganisms should be allowed provided the criteria noted above are met. However, infection (as objectively defined in a recognized standard manner) and not infection surrogates (such as colonization or surface/hand contamination) should be the outcome measure.

h. The contact time to obtain infection reduction must be clinically and operationally reasonable and feasible for a given clinical situation. It is not meaningful to provide an infection reduction claim with a contact duration that could not be reasonably achieved in a busy clinical setting. In general, a contact time of three minutes or less is optimal. We believe this goal to be achievable if such studies are conducted using the quantitative testing program EPA has proposed to replace the current AOAC testing.

i. There should be use instructions to include: appropriate use dilution (if applicable); contact time (how long the surface should remain visibly wet); use contraindications (e.g., not for skin, glassware, dishes, clothes, wood, rubber, painted surfaces, silver, aluminum, etc); use/application instructions
(including appropriate protocols and steps) for achieving infection reduction; precautionary statements and hazard warnings; emergency first aid (e.g., if in eyes); proper storage and disposal; etc. These instructions should mirror the manner in which the product was used in the studies to achieve the stated efficacy in infection reduction.

2. What tools, aside from product – specific efficacy, do you think the Agency should consider for quantitative/qualitative infection reduction claims?

The product should demonstrate a decreased rate of infection in at least two well-conducted clinical trials and the reduction should be clinically and statistically meaningful. Products must be safe.

3. Recognizing the multiple infection control programs (that vary within the same region), do you think infection reduction claims are potentially misleading? Considering the varied infection control programs, are quantitative claims reproducible?

As with drug studies submitted to the FDA, we recommend the EPA require at least two independent trials that demonstrate the specified efficacy. The label claim should be restricted to the appropriate setting and population in which the efficacy is demonstrated as noted in the example above.

4. How does your facility/organization define infection control programs?

Infection control programs are organized programs dedicated to the control and prevention of healthcare-associated infections with the following: mission statement; dedicated staff who are appropriately trained; budget; program objectives, goals and indicators based on a risk assessment of the organization’s patient population and infection risks; policies/procedures; surveillance (CDC criteria);and evidence-based performance improvement initiatives.

5. As infection control programs vary from facility to facility, what components are inherent to all infection control programs? What components of an infection control program are critical to support infection reduction claims?

Critical components of a comprehensive infection prevention program include dedicated human and financial resources as well as qualified and trained staff, surveillance, policies and procedures involving pertinent departments needed to execute the specific protocols (e.g., environmental services) are needed to implement evidenced-based guidelines.

6. If the proposed infection reduction claims are quantitative or qualitative, what supporting documentation should the Agency consider?

See Q.1 regarding qualitative claims. For quantitative, consider at least two appropriate clinical, independent trials with well-described goals, methods, outcomes, and statistics and published in the peer-reviewed literature. Two recent examples of studies with rigorous methodologic design, high-grade quality, and clinically meaningful results involving topical antimicrobials are: Bode LG, et al New Engl J Med 2010;362:9-17 and Darouiche RO, et al., New Engl J Med 2010;362:18-26. We’d be happy to provide other examples involving antimicrobials intended for environmental surfaces published in the peer review literature or, conversely, a critique of evidence that lacks clinically meaningful impact if helpful. These citations might be useful as points of discussion in an advisory meeting to discuss the proposed criteria.

7. What microbes (bacteria, viruses, fungi etc.), if any, should be exempt from infection reduction claims?

No microorganisms should be exempt but studies submitted should reflect true reduction in incidence of infection. Surrogates such as colonization or surface contamination should not be used for infection reduction claims.
8. Are peer-reviewed publications sufficient to support infection reduction claims? If so, what parameters (case-studies, observation studies, etc.) should exist in the cited studies?

Yes. The studies must be designed to provide as high a grade of evidence as possible. The best and most definitive of these are double-blind, randomized trials. Levels below this in rank order include systematic reviews, randomized cluster series, time series analysis. Observational studies, e.g. “before – after”, fall below these, and, unfortunately, are the predominant methodology in much of the literature. These lack rigor and are subject to bias and therefore are not as definitive. Last, case studies or anecdotal reports are low to very low quality and should not be a basis for registration. Umscheid and others have published a useful description of scoring quality of evidence CDC uses to create recommendations for prevention of HAIs. This might be worth reviewing. The article reference is provided below. (1) Again, the proposed types of studies and quality of evidence needed might be useful in a discussion forum.

9. If the Agency grants infection reduction claims, what additional use directions/label verbiage should be included on the product label?

Any safety information and use restrictions (needs to be evaluated on a case-by-case) should be included, as well as a summary description of the protocols and tools or equipment used (e.g., cotton cloths vs. microfiber vs. pop-up wipes) to achieve the infection reduction outcome. We note that use of microfiber specifically may have a different effect than use of a cotton cloth or pop-up wipe.

10. Should a training program for the end-user be a requirement of infection reduction claims? If so, what components of a training program should the Agency consider?

The need for a training program will depend upon the complexity of the use process. Use instructions should accompany the product and include: appropriate use dilution (if applicable); contact time (how long the surface should remain visibly wet); use contraindications (e.g., not for skin, glassware, dishes, clothes, wood, rubber, painted surfaces, silver, aluminum, etc); use/application instructions (including appropriate protocols and steps) for achieving infection reduction; precautionary statements and hazard warnings; emergency first aid (e.g., if in eyes); proper storage and disposal; etc. These instructions should mirror the manner in which the product was used in the studies to achieve the stated efficacy in infection reduction.

11. What impact do you anticipate from the healthcare community if infection reduction claims are granted?

The healthcare community will preferentially use the product if cost effective and feasible, reproducible results are achieved and deemed effective based on a facility-wide risk assessment employed by the infection preventionist(s). If criteria for registration could move to those outlined above, the healthcare community would be receptive to such label claims.

12. There is a paper attached with this letter. Is this type of documentation sufficient to support infection reduction claims? Please provide additional comments.

We have reviewed the paper provided and the other articles provided by the Antimicrobials Division. The two conducted in healthcare facilities have inherent flaws and weaknesses and are observational in nature. Therefore they would not meet the criteria we have outlined in our response to question 1 above. The others are from non-healthcare settings but also are observational in nature and used endpoints lacking clinical or microbial precision on which to base the infection reduction claims. The references are appended in a separate file for convenience. (See Appendix Q12)

Q.12 Appendix Reference Analysis

Reference 2:

This ten-year old, well known study carried out in a highly respected institution was one of the first to carefully evaluate the role of the environment in C. difficile (CD) transmission. Studies published over the past ten years increasingly support the importance of the environment in CD transmission, and this was a rare study which evaluated post-intervention trends and attempted to carefully analyzed antibiotics as a confounder.

Process - Cleaning agent versus cleaning practices

Cleaning agent
1) Hypochlorite vs. Quat Although not specifically stated, it would appear that the implementation of the special cleaning protocol using 1:10 hypochlorite was initiated in response to the recognition of ongoing high rates of CDAD on the BMT units, since the authors do not indicate that interventions to improve disinfection practice with the quaternary disinfectant were attempted prior to the use of hypochlorite. For this reason it cannot be assumed, a-priori, that the quaternary disinfectant was not working; one can only infer that the high rate of CDAD had been continuing for a period of time prior to intervention.

2) “Protective effect”? At the beginning of the discussion the authors state that, “Our data show a protective effect of hypochlorite solution against the CDAD acquisition in an area of high endemicity in an acute care hospital.” This statement represents an incomplete and somewhat misleading conclusion, since it fails to consider the likely importance of improved cleaning practice during the intervention period. Further this “protective effect” should have been limited to the bone marrow transplant (BMT) unit only—not the hospital. That is, the only unit showing significant change was the BMT unit. Indeed, the authors subsequently modify this statement later in their discussion by stating, “Overall, our findings confirm an association of unbuffered 1:10 hypochlorite solution with reduced CDAD rates in a unit with high prevalence rates.” (emphasis added).

Cleaning/monitoring protocols
1) Cleaning: Although there was a fairly striking and significant improvement in the CDAD rate in the BMT unit following implementation of a diluted hypochlorite protocol, it is unlikely that hypochlorite use alone accounted for the difference, given the authors’ statement (page 996 – Interventions) that:

- “Nursing, environmental services managers and staff were instructed about the purpose and procedure for using hypochlorite by the infection control specialist, and the housekeeping staff was instructed to use 1:10 hypochlorite solution that was mixed fresh daily.”
Adherence to the new hypochlorite protocol was monitored by the infection control specialist, who periodically contacted the housekeeping staff to determine whether they were aware of the CDAD status of patients and if the hypochlorite was being used properly to clean patient rooms. Therefore it is highly likely that improved cleaning practice played a significant role in the decrease in CD transmission subsequently documented. This level of supervision and oversight is neither typical nor feasible outside of a special investigation.

2) Monitoring cleaning practices: Although the rebound in CDAD cases after discontinuation of the protocol was attributed to the failure to continue to use hypochlorite, it is of note that the special hypochlorite cleaning protocol and monitoring of practice compliance would appear to also have been discontinued at that time. A deterioration in the thoroughness of cleaning could well have accounted for a contamination of the near-patient environment and the subsequent rebound in cases.

Indeed, the fact that there was a gradual but very steady increase in transmission over the four months following the discontinuation of the hypochlorite protocol in June, 1997 very much supports such a possibility. If the discontinuation of the hypochlorite alone was causative, rates should have increased almost immediately after bleach use was discontinued, since it can be assumed that the incidence density of newly introduced cases to the unit probably remained the same over time.

Before/after studies are always difficult to assess when so many variables do change in time—and in this case cleaning staff turnover-training also becomes a critical variable to this study’s outcome.

C difficile (CD) and VRE

In retrospect considering the changes in CD over the past ten years, there are some other related issues that raise more questions than answers. The work was done 1996-97 (pre-2000) before the current epidemic strain of CD (NAP1/BI/027) was rampant. That may or may not have had an impact. In any case the environmental C. difficile prevalence was not measured as noted below.

It is very odd that VRE emerged during the study and only seemed to respond to thequat plus more attention to mechanical friction—not dilute hypochlorite. It is counter-intuitive that a quat alone was more effective against VRE.

Antibiotic and antineoplastics volume

Table1 shows that for the one unit of alleged effective impact of dilute hypochlorite, i.e., the BMT, there were significant differences in the volume of use of antibiotics and antineoplastics and volumes were altered during the study. We know both antibiotics and antineoplastics induce CDAD. Could this have explained changes in incidence of CDI; at least partially? Most importantly and puzzling is that if the change was due to hypochlorite alone, why wasn’t there more impact on other units since Table1 does show similarity in populations before and after the interventions? This would mean that any conclusions of this study are only applicable to BMT units—and no other patient units. This is a major anomaly if the effect is solely due to dilute bleach.
This well intentioned study did not measure a critical variable ("thoroughness of cleaning") as we would do today. With today's tools we could truly more clearly answer the question of measuring thoroughness of cleaning and better distinguished between the affect of the cleaning agent distinct from cleaning protocols.

Reference 7

Wilcox. This time-interrupted series consisted of an evaluation of the impact of hypochlorite based cleaning of two wards with high endemic CDAD rates. As noted earlier on one ward there was a modest (p < 0.05) decrease in new infections while on the other ward, no impact with the modification of disinfection practice was recognized. Environmental contamination, both before and after the use of bleach, was the same. The fact that environmental contamination was primarily assessed on floors may well have limited the analysis of the clinical impact of the intervention. The thoroughness of hygienic practice was not evaluated.

References 2 and 7
Both Mayfield and Wilcox illustrate there is no single, "magic bullet" but there are interventions, some that likely relate to Hawthorne effect, that all play key roles in assessing their impact on patient safety.

References 3, 4, 5, 6 - Community-based studies

The community-based studies all did multiple interventions and were vulnerable to major Hawthorne effects. The environments of these additional investigations, child care facilities and domiciles, are not representative of the types and quantity of microbes encountered in healthcare facilities. In fact the predominant outcomes assessed were likely illness caused by respiratory viruses. The transmission of these infections is even more complex and reservoirs for these are as abundant in the community, workplace, social gatherings, as they are in any one facility or domicile. We don’t feel these add any more to evaluation of any particular disinfectant and all share the same weakness of a multitude of other variables that might explain reductions in illness associated absenteeism. What role a particular disinfectant played is very difficult to unwind from the other important factors. Specifically:

Kotch. This study related to evaluation of child day-care centers (CDCCs) in the late 1980s. Rates of illness in children was monitored twice weekly by interviewing parents. Two groups of child care centers CDCC’s were evaluated. The intervention group had three hours of focused education related to environmental hygiene issues and ongoing evaluation of hygienic practice during the study. The second group served as a control. There was no statistically significant difference in diarrheal or respiratory illness between intervention and control sites. Although not discussed by the authors, several confounders as well as the limits of a simple educational intervention could have
explained their findings. While this prospective match control study was well designed with good illness data collection, actual hygienic practice was not evaluated.

**Krikrilov.** This interrupted time series study of a single location used questionnaires to document parental recollections of their children’s illnesses during the year prior to the CDCC implementing educational and procedural changes. “Compliance with recommended hygienic practices” (not detailed further) was felt to be good but was not measured prior to the intervention year. Major confounding variables such as the incidence density of infection prior to and during the study were not evaluated. Given these limitations, the results of the study must be considered inconclusive.

**Larson.** This study consisted of an ongoing evaluation of household hygienic practices and beliefs over a year while monitoring the incidence of respiratory and diarrheal disease in household members. The possibility that practice changed over time as a result of the study was not evaluated. There were two hygienic practices, washing clothes with warm water (p = .02) and washing clothing with bleach (p = .001), which appeared to favorably impact the incidence of presumed infectious illness in the households. Due to limitations of the study, multivariate analysis could not be performed.

**Uhari.** This study from Finland evaluated the impact of hygienic education and several enhanced practice interventions at ten CDCCs in Finland. Reported illnesses were monitored over a year and compared with ten non-intervention centers. Detailed family education was done at the intervention centers but not the control centers. During the study the children at the intervention centers had substantially less respiratory illness and somewhat less diarrheal illness but the study was not able to evaluate the impact of specific interventions nor was it able to assess the impact of enhanced hygienic practices in the home vs. the CDCC.