1275 K Street, NW, Suite 1000
Washington, DC 20005-4006
Phone: 202/789-1890
Fax: 202/789-1899
apicinfo@apic.org
www.apic.org

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Ms. Leslie Kux
Assistant Commissioner for Policy
U.S. Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, MD 20852

Re: Docket No. FDA-2012-N-1040, Comments to FDA on Antiseptic Patient Preoperative Skin Preparation Products

Dear Ms. Kux:

The Association for Professionals in Infection Control and Epidemiology (APIC) appreciates the opportunity to provide input to the U.S. Food and Drug Administration (FDA) on how to address microbial contamination of patient preoperative skin preparation drug products. APIC is a nonprofit, multidisciplinary, international organization representing over 14,000 Infection Preventionists (IPs), whose mission is to create a safer world through prevention of infection.

In the past, intrinsically contaminated antiseptics have caused infections and death.[1] Most recently, alcohol prep pads (APPs) intrinsically contaminated with *Bacillus cereus* were associated with cellulitis and bacteremia in pediatric patients in Colorado,[2] leading to a nationwide recall.

Healthcare has changed drastically since development of standards for manufacturing of antiseptics. As an example, over 800,000 people receive treatment for end-stage renal disease in the United States.[3] Five thousand people receive stem cell transplants each year.[4] Both conditions require the long-term use of invasive devices, which must be repeatedly accessed for care. The process of accessing these devices includes the use of APPs to reduce microbial contamination potential.

APIC has supported the use of unit-dose patient supplies in the past and there are unit-dose antiseptics available on the market. However, there are still instances where multiple dose types of prepping agent containers are used. Both non-sterile single-use, as well as non-sterile multiple-use dosing containers can provide a source of contamination for the skin prepping process.

Care once restricted to the inpatient setting, such as intravenous antibiotics and feeding, is now routinely administered in the home setting. Complex wounds are being managed in outpatient clinics and by home health agencies. It is in this context that the APIC responds to the following questions from FDA.

A. Intrinsic Contamination

1. *Are healthcare providers and consumers aware that patient preoperative skin preparations generally are not sterile? What measures can be taken to increase awareness of this fact?*

   Response:
   APIC believes that healthcare providers and consumers alike are not aware that patient pre-operative skin preparations are generally not sterile. We recommend that products be clearly labeled so it is obvious to the consumer if the product is sterile or not sterile. Consumers and healthcare personnel assume that APPs are sterile because non-sterile APPs are not labeled as such. A recent recall attributed to contamination with *Bacillus cereus* and *Bacillus* species was associated with the use of APPs that did not indicate that the product was not sterile and the users assumed they were sterile.[2,5]

2. *In light of the adverse events associated with contamination of patient preoperative skin preparations, should all such products be manufactured sterile?*

   Response:
   APIC believes that all skin preparation products should be manufactured to be sterile. While we are aware that research and work needs to be done to enable the production of sterile prep agents, APIC believes the time has come to begin those processes to provide sterile prep products. These agents are being used to eliminate, to the best of the healthcare sectors ability, the microbiological contamination of the skin prior to an invasive procedure (intravascular lines to surgical incision sites). These agents should provide protection rather than possible contamination.

   It should be noted that, while alcohol alone is rarely used as a surgical skin preparation, it is used extensively for other purposes in healthcare. With national and global efforts to decrease central line-associated bloodstream infections (CLABSIs), the use of APPs to disinfect the ports on intravenous (IV) catheters is instrumental in the prevention of these infections. Targeted efforts have been instituted to assure that healthcare personnel are scrubbing IV catheter ports/hubs whenever they enter the IV catheter to instill intravenous medication and fluids as well as removing blood samples, etc. This procedure is done thousands of times a day at healthcare facilities and it is essential that these products be sterile to avoid the installation of organisms from intrinsically contaminated products, especially those that are currently manufactured as non-sterile.

   Additionally, as has been seen frequently in recent events, the dependability of sound environmental and aseptic conditions during the manufacturing process is not controlled to the level required, and therefore heightens the concern for product contamination. The need for more stringent processing and product sterility, along with evidence of lack of product contamination at the completion of the manufacturing process is necessary.

3. *What can FDA do to help manufacturers overcome challenges in this area?*

   Response:
   APIC believes the FDA needs to set clear science-based expectations and guidance for manufacture and sterility of skin preparation products. It is incumbent upon the FDA to provide oversight, enforcement, and adherence to those processes that enhance patient safety.

This could include increasing the requirements for product testing to include organisms that are currently not part of the testing protocol. The continued contamination of surgical skin products[6,7,8,9] and other products[10,11,12] used in healthcare with *Burkholderia cepacia* [4-11] as well as *Bacillus* species indicates that existing methods are insufficient to detect low levels of microbial growth. There needs to be a critical look at these testing criteria for manufacturers followed by development of enhanced requirements to cover the recurring contaminating organism culprits as well as the resistant organisms of great concern in healthcare today.

The FDA needs to provide an expeditious review and approval process to aid the manufacturers in moving through the approval mechanisms.

B. Extrinsic Contamination

1. *Products manufactured sterile can be contaminated as soon as they are opened for the first time. What steps can be taken to reduce the risk of extrinsic contamination of patient preoperative skin preparations?*

   Response:
   We recommend that manufacturers produce single-use size containers, which are cost effective to use, as well as provide appropriate labeling for sterility factors, proper storage, and use and disposal guidance. It would be a proactive patient safety design for manufacturers to develop product that would not allow a previously opened product to be reclosed, or to place a container down on a surface in order to avoid contamination caused by contact with that surface.

   Healthcare providers need to adhere to proper storage, use and disposal guidance. Internal inspections of healthcare facilities should include attention to adherence to expiration dates proper disposal after opening, and proper aseptic product use. Additionally, surveillance by healthcare providers for infections and complications related to improper use or contaminated products needs to occur.

2. *Excluding the use of these products before surgical procedures or injections, are these products used for other purposes in healthcare or home settings (e.g., wound care or maintenance care for indwelling catheters)? If so, what is the extent of these uses in healthcare or home settings? What settings or uses comprise the majority of utilization for single-use products? What settings or uses comprise the majority of utilization for multiple-use products?*

   Response:
   These products are and can be used for other purposes in healthcare settings and home care, such as wound care and maintenance care for indwelling catheters and invasive lines. All of those uses would benefit from availability of sterile, single-use product lines.

   APIC strongly encourages manufactures to provide these products in single-use packages/containers to prevent products from getting extrinsically contaminated during use and also to prevent them from being used on multiple patients. It would also be important to be able to provide such products in a cost-effective manner for the users to avoid the temptation to re-use products packaged in larger containers due to financial constraints.

3. *To what extent are multiple-use containers of patient preoperative skin preparations further processed (e.g., diluted, mixed, or repackaged for subsequent redistribution) in healthcare or home settings? If these products are diluted, mixed, or repackaged, are they handled aseptically? Why are these products diluted?*

   Response:
   Healthcare providers should follow manufacturer's directions for dilution, mixing and repackaging. The expectation would be that such manipulation would be performed aseptically.

   APIC does not support the adulteration of any product outside of the manufacturer's directions or recommendations.

4. *Should patient preoperative skin preparations be marketed only in single use containers? If single and multiple use containers are permitted, in which ways could single-use containers be clearly distinguished from multiple-use containers (e.g., by labeling, size, volume, presence/absence of applicator)? What technical and practical challenges would manufacturers and users face should there be regulatory requirements that limit package sizes for multiple-use patient preoperative skin preparations?*

   Response:
   APIC believes that patient preoperative skin preparations should be manufactured and marketed in single-use containers, with volume/size choices and proper labeling. These single-use containers should be obtainable without increased cost to the patient or the institution. We do not support or encourage use of multiple-use containers. Single-use containers should be designed in such a way that multiple-use is not possible.

5. *Can product labeling, for example, instructions to "discard X days after opening," be used to reduce the risk of adverse events associated with extrinsic contamination of patient preoperative skin preparations? How could a "discard by" date be established for individual products and how meaningful would such a date be in the context of current practices?*

   Response:
   Product labeling for discard dates after opening a product could be helpful to reduce microbial growth opportunities, but APIC continues to support single-use containers of appropriate, cost-effective sizes, to avoid opened products sitting on shelves with the opportunity for contamination: an expiration date alone does not eliminate the possibility of extrinsic contamination of a multi-dose product.

   If "Discard by x Dates" are to be established, those dates should be verified by pre-market research based on microbial growth observations and testing of open product. Only then could such a practice be meaningful and appropriate for patient safety

6. *Are healthcare facilities or other entities providing information or training on safe use of multiple-use patient preoperative skin preparations, or taking other steps to reduce the risk of extrinsic contamination of these multiple-use products? If so, please describe these efforts and any available information on their effectiveness.*

Response:
APIC believes that healthcare facilities in general do train and educate to proper aseptic techniques in handling any patient product, single-use or multiple-use. However, ongoing reinforcement of proper procedures is needed, especially in non-acute healthcare settings that may not be overseen by internal and regulatory agencies to help enforce these aseptic approaches.

Some healthcare facilities, despite cost escalation and in the absence of single-use products, have begun to use multi-use designated products as single-use only in an attempt to eliminate possible contamination risks. This adds to the cost of healthcare for patients.

APIC commends FDA for its efforts to protect patients from contamination resulting from use of nonsterile skin preparation products, and we look forward to continuing to work with the agency to find solutions that will prevent infections.

Sincerely,

Patricia S. Grant, RN, BSN, MS, CIC
2013 APIC President

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