

**Milliken & Company Response to:**  
**Draft Guidance for Industry and FDA Staff**  
**Premarket Notification [510(k)] Submissions for Medical Devices**  
**that Include Antimicrobial Agents**

**Clarifications:**

Page 4 and Table 1 – The consideration of “same” includes several narrow parameters. For example:

- On page 4, line 23, states that a new device must contain the same concentration of antimicrobial agent as the predicate. Do the concentrations have to be identical? If not, how close is acceptable?
- On page 4, line 28: In terms of indications for use and “same” anatomical site, what is the required specificity? For example, is “skin” considered the same anatomical site regardless of location on the body? Additionally, would antimicrobial additives used in already registered medical devices require the same documentation as antimicrobial additives never before used in a registered medical device?
- On page 4, line 32: How specific must the device design be for it to be considered the “same”? For example, would polyester fabric be considered the “same” as nylon fabric? What is meant by geometry? Is geometry restricted to general shape or does it include specific measurements such as surface area or thickness of the device?

Overall, it appears these parameters are so specific, that for a new device to fall under the “same” category, it would essentially be identical to the predicate. If this is the case, why would a new 510(k) be required?

Page 7, line 25 – Please clarify the need for identifying individual microbial subtypes as part of the rationale for adding the antimicrobial agent to the device. We suggest that identification of the organisms to the species level should be sufficient as device related infections are linked to certain species not to specific microbial subtypes within a species.

Page 10, line 7 – How is “an implantable medical device” defined? Would a CVC or Foley catheter be considered an implantable medical device?

Page 10, lines 15-20 –What is the purpose of determining the MEC? The objective of this measurement is important as it affects the recommended dose in the device. If the purpose is to minimize the opportunity for development of microbial resistance, then the dose of antimicrobial agent should far exceed the MEC. If the goal is to minimize risk to the host, then the dose should equal or barely exceed the MEC.

Page 10, line 16 – What is meant by “effective” in the MEC? Is it speed-of-kill, the maximum log reduction, duration, or efficacy?

Page 10, lines 18 – 10 - What would the FDA suggest as an approach to calculate the MEC? Since testing must be conducted on the finished device, it is a concern that the

determination of an MEC would require testing different concentrations, formulations or applications of antimicrobial treatment to establish an MEC for every assay that is “...consistent with clinical use of the device.”

Page 12, line 36 – How do you define a “clinical isolate”? Can clinical isolates be sourced from a culture collection such as ATCC as long as the original isolation was from a clinical source? Without access to public culture collections, it is uncertain how device manufacturers could obtain access to clinical isolates. Please clarify the need to use isolates within 1 – 2 passages from original isolation. Is that requirement related to the number of subcultures performed before entering the culture collection bank or to the number of subcultures performed in the testing lab prior to the actual inoculation of the device?

### **Comments/Suggestions:**

Page 2, line 22 – Suggest to replace “any” with “many”. We understand the concern regarding the selection for resistant microbes through the use of antimicrobial agents. However, it is widely recognized that microbial populations are much more likely to develop resistance to antibiotics than to antimicrobials (such as silver or iodine) since antimicrobials have lower target specificity than antibiotics.

Page 7, line 17 – The term “species” covers both the genus and the specific epithet; for example the species *Staphylococcus aureus* is made of the genus “*Staphylococcus*” and the specific epithet “*aureus*”. Suggest to replace “...to the genus and species level.” for “...to the species level.”

Page 7, line 17 – Suggest to add “... species level. Target pathogens should include the same species of microbes that are most prevalent contaminants of the device during normal use.”

Page 7, line 25 - Recommend to change “bacterial” to “microbial” as some contaminants may include fungi or virus.

Page 7, line 25 –Suggest that identification of the organisms to the species level should be sufficient as device related infections are linked to certain species not to specific microbial subtypes or strains within a species.

Page 10, lines 15-20 – Suggest that the degree of effectivity of the treated device could be established with reasonable “bridging” experiments that compare *in vitro* efficacy using established standard methods to the release or availability of the antimicrobial agent in or on the device.

Page 14 –Practically, labeling space for devices is at a premium and it would be extremely difficult to add all of the suggested items. In addition, if the treated device has been approved by the FDA, it is unclear why the specific chemical name, concentration,

and amount released from the antimicrobial would be required to be presented on the device label. Historically, the device labeling has focused on the indications and contraindications for use. For antimicrobial treatments, intended solely to reduce colonization of the device surfaces (not to deliver drugs or therapeutic agents), it is suggested that certain data and information should not be required on device labeling. Examples of information that we believe should not be required include spectrum of activity and concentration of the antimicrobial agent. However, we agree with the requirement to include warnings about the antimicrobial treatment or contraindications to the use of the treated device.