

October 17, 2007

Division of Dockets Management
HFA-305
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, MD 20852

Re: Docket No. 2007D-0201
Draft Guidance for Industry and FDA Staff: Premarket Notification [510(k)] Submissions
for Medical Devices that Include Antimicrobial Agents

Dear Sir or Madam:

The Center for Biofilm Engineering (CBE) is a research institution at Montana State University which investigates attached microbial communities (biofilms) and their impacts in medical and industrial contexts. We have been asked by several of our industry contacts to act as a focal point for responses to the Proposed Draft Guidance referenced above. Submitted herewith are comments concerning this document. We appreciate the opportunity to respond to the Agency's request for comments.

Overall Comments

1. The Proposed Draft Guidance contravenes the classical definition of an antimicrobial agent as defined by Goodman & Gilman's The Pharmacological Basis of Therapeutics, Ninth Edition. Based on their expert opinion, an antimicrobial is an agent that: (1) inhibits the synthesis of bacterial cell walls; (2) acts directly on the cell membrane of the microorganism, affecting permeability and leading to leakage of intracellular compounds; (3) affects the function of the 30S or 50S ribosomal subunits to cause a reversible inhibition of protein synthesis; (4) binds to the 30S ribosomal subunit and alters protein synthesis, which eventually leads to cell death; (5) affects nucleic acid metabolism; (6) functions as an antimetabolite to block specific metabolic steps that are essential to microorganisms; and (7) nucleic acid analogs which inhibit viral enzymes that are essential for DNA synthesis, thus halting viral replication. Within the Proposed Draft Guidance, Part V. Device Description, subpart A. Indication for Use, the following statement is made: "FDA believes the following indications may be appropriate for devices that include an antimicrobial agent: (1) reduces or prevents device-related infections, and (2) reduces or inhibits microbial colonization on a medical device". An agent that reduces or inhibits microbial colonization on a medical device does not, in our opinion, meet the classical definition of an antimicrobial agent. It is our opinion that an agent which reduces or inhibits biofilm formation is in a separate, but related class of microbial actives. Therefore, we ask that the title of the Proposed Draft

Guidance be changed to include, in addition to the words “antimicrobial agents”, the words “microbial actives” which would include quorum sensing agents. This change will reflect the additional mechanisms of action that are referenced in your document, but are not antimicrobial in nature.

2. Realizing that these are guidelines, serving a very wide variety of applications and products, it would be helpful if the guidance were clearer on what is required from a non drug, non combination product, (510K submission) versus a combination product needing clinical trials and a PMA submission.
3. There is concern that the Guidance may require that a company reveal more detail regarding intellectual property than they might be comfortable with. A compromise approach would be for industry to submit what they are comfortable with, and then if the Agency needs more information, they are free to request it and discuss it with the company.

Specific Comments

1. Page 14 / lines 19-20, 21-22, 33, 34, 35, 36

If there is no claim as to the therapeutic benefit/effect for patient, are these necessary/pertinent? The manufacturer would have to prove safety of these materials via toxicology, pharmacology, etc, internally to support our submission but is it necessary for proper use of the device? There is evident potential for IP to be divulged.

2. Page 14/ line 29

This statement should be amended to read "**Known** contraindications for use in the presence of certain drug therapies" As written, this statement could become burdensome if manufacturers were expected to test their antimicrobial agents with many different drug therapies used clinically. This would likely be a current literature search or assessment, attached to the Toxicology assessment.

3. Table 1, Descriptive Characterization of the Agent – ‘Modified’

Does the term “Pre Clinical” meant to be animal testing or bench/in vitro testing or both?

4. Section VI: Characterization of the Antimicrobial agent

This section needs more clarity. Some items in this section refer to characterization of antimicrobial agent as it is applied on a device. Some items refer to the agent itself.

- A. Identity and formulation: Identity is agent specific; formulation is as it is going to be applied on a device
- B. Concentration – as applied onto a device
- C. Method of application – on a device
- D. Mechanism of action –agent as applied on a device (state if agent is leaching or bound)
- E. Antimicrobial activity spectrum profile: Agent specific. Information on antimicrobial spectrum of an agent in literature (publications, NDA, DMF etc) or derived from

standardized methods is Minimum Inhibitory Concentration (MIC) and Minimum Bactericidal Concentration (MBC), defined as weight/volume.

- F. Release kinetics – as applied on a device
- G. Minimum effective concentration (MEC) – as applied on a device in weight per area
- H. Toxicity: agent specific (comparison device application related)

5. Page 10: Section G; Minimum Effective Concentration (MEC):

This type of information may be developed during product development, not using a finished product. Typically, during product development, a manufacturer may utilize information available such as MIC/MBC or MBEC (minimum biofilm eradication concentration) for an agent and relate it to release kinetics or concentration per area. For different organisms this value is going to be different (Example, for a broad spectrum antibiotic, MIC/MBC values are different for different organisms). This information is utilized for establishing product specifications having total concentration X times more than minimum highest effective concentration observed to cover claims for all pathogens of interest and also to cover for differences between in vitro vs. clinical environment. The product specification will have a range and finished product may be tested for various organisms for desired claims as required under section D Page 12 – sub section 1: Bench Testing. The finished product at nominal or lower spec level may be tested in an animal model. However, MEC values may not be generated on a finished product.

6. Page 12; Bench Testing: (lines 34-39)

- A. The agency should elaborate on their current thinking on a requirement of X number of strains of one organism that should be tested.
- B. The agency should elaborate on their current thinking on minimum level of demonstrated efficacy (minimum % or log difference between modified device and control device)
- C. The agency should elaborate on their current thinking on acceptable storage conditions of clinical isolates

7. Page 12: Bench Testing (Lines 41-42)

The bench testing on a finished product is usually done using a lower or nominal specification values. The results may establish that the product is effective at one selected concentration and not determine what the (minimum) effective concentration is and what the relationship is when concentration is increased.

8. Page 13: Section 2 – animal studies

The agency should provide more guidance on this requirement to conduct animal studies. Under what conditions animal study is absolutely necessary? Is agency going to participate in protocol development?

9. Page 4, the term "modified".

As defined, won't most if not all submissions be defined as "modified"? If so, what's the point of having a "same" category? In other words, the definition of "same" is very narrow, which probably is the point but it's not useful if it's too narrow.

10. Section 4 in general.

Suppose the antimicrobial agent is the "same" but the device is "modified" (geometry, etc) how is the "new" device classified - same or modified? The concern is that if it's "modified" then the requirements for "modified" must be followed which include antimicrobial characterization details which in this case would be non value added as the agent is the "same". For this specific instance, the guidance is not clear. I think this case may come up more often than not when companies are trying to apply antimicrobial "A" on to multiple devices which may be "similar" but not the "same" by the definitions in this guidance.

We appreciate the opportunity to offer these comments on the Draft Guidance.

Sincerely;

A handwritten signature in black ink, appearing to read "Paul Sturman". The signature is fluid and cursive, with a long horizontal stroke at the end.

Paul J. Sturman, Ph.D.
Industrial Coordinator
Center for Biofilm Engineering