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October 16, 2007

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

Re Response to Docket No. 2007D-0201

Dear Sir or Madam:

On behalf of AdvaMed, the Advanced Medical Technology Association, I am pleased to submit these comments in response to the United States Food and Drug Administration publication of "Draft Guidance for Industry and FDA Staff: *Premarket Notification [510(k)] Submissions for Medical Devices that Include Antimicrobial Agents*" as published in the Federal Register: July 19, 2007 (Volume 72, Number 138, page 39630-39631).

AdvaMed member companies produce the medical devices, diagnostic products, and health information systems that are transforming health care through earlier disease detection, less invasive procedures and more effective treatments. Our members produce nearly 90 percent of the health care technology purchased annually in the United States and more than 50 percent purchased annually around the world. AdvaMed members range from the largest to the smallest medical technology innovators and companies.

AdvaMed member companies are dedicated to ensuring the safety and efficacy of the products they manufacture. Medical devices that include antimicrobial agents as components of the device offer an opportunity to improve healthcare and provide benefits to patients.

Thank you for the opportunity to provide comments on the draft Guidance. AdvaMed fully supports FDA's efforts to ensure that the use of antimicrobials in medical devices cleared through the 510(k) process benefits patients and that their



use does not pose an unacceptable risk. However, AdvaMed has concerns about certain provisions of the draft Guidance.

Comments

Attachment A provides a list of comments on the Guidance and a rationale for each comment.

We have two major concerns. We believe the Guidance should allow manufacturers to determine if the use of an antimicrobial agent provides an indication for use of their device or if it simply serves as a device attribute. Manufacturers may include an antimicrobial as a performance characteristic of the device that does not affect the indications for use. For example, the addition of an antimicrobial agent that inhibits colonization of microbes on the surface of the device does not alter the indications for use of the device.

The Guidance should not require specific manufacturing information. Manufacturing information is generally considered confidential and is carefully protected. Manufacturing information for predicate devices is unavailable to competitors, and therefore, cannot be used to draw a comparison between the new device and the predicate. Most importantly, manufacturing information is not required in 510(k) submissions.

Conclusion

AdvaMed supports the FDA's efforts to provide guidance to industry on the information necessary to support premarket notification submissions [510(k)s] for medical devices that include antimicrobial agents. We thank FDA for the opportunity to submit these comments.

If you have questions or would like clarification, please feel free to contact me at 202-434-7220 or rdempsey@advamed.org.

Sincerely,



Ruey C. Dempsey
Director
Technology and Regulatory Affairs

ATTACHMENT A
ADVAMED COMMENTS

AdvaMed comments on Draft Guidance for Industry and FDA Staff ***Premarket Notification [510(k)] Submissions for Medical Devices that Include Antimicrobial Agents***

No. – Comment number

Page No. – Guidance page number

Line(s) No. – Line or lines numbers of the guidance

Change – Proposed change to the guidance

Rationale – Reason for proposed change

No.	Page No.	Line(s) No.	Change	Rationale
1	1	19	Add at the end of the sentence “or as a performance characteristic”.	Some manufacturers may not consider the action of an antimicrobial agent an indication for use. They may use the antimicrobial as a performance attribute in the same way they choose other materials to enhance performance (e.g., use of polyurethane rather than silicone elastomer to enhance flexibility).
2	3	5	Include a more detailed definition of antimicrobial agent and give examples.	The guidance appears to focus on antimicrobial agents that are drugs; acknowledge that antimicrobial agents can be a chemical compound or a physical agent (e.g., silver).
3	3	11	Add in-vitro diagnostics to the list of exclusions.	IVD products such as reagents and IVD electrodes often contain antimicrobial agents. These do not contact the patient, and therefore, raise none of the concerns the guidance addresses.
4	4	18	Clarify that the “same indication for use” may not include an antimicrobial indication.	Some manufacturers may have the same design and same antimicrobial agent but may not choose to claim antimicrobial action as an indication.
5	4	24	Delete the requirement for method of application; provide it when appropriate.	This information may not be known about the predicate device. This is manufacturing information and may not be revealed in the predicate device labeling.

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No.	Page No.	Line(s) No.	Change	Rationale
6	4	26	Provide clarification or example of what information must be provided.	
7	7	34	Provide more detailed description of "information" required/recommended.	The term "information" is not informative of the expectations.
8	7	10	Rephrase to reflect "if the indication for use includes action of an antimicrobial agent".	Allow for manufacturers who do not state indications related to the antimicrobial agent.
9	7	17	Require a more general description of the target population (e.g., gram positive bacillus) and a more specific one as appropriate.	Genus and species are too specific and would require exhaustive testing that would be overly burdensome.
10	9	4	Clarify the requirements stated in this section regarding concentration (versus content or amount) for different models/sizes.	Concentration normalizes for all sizes.
11	9	6	Replace "calculate" with "determine."	Actual measurement may be the method used rather than theoretical calculation.
12	9	7	Clarify. Perhaps replace "any" with "the."	The use of "any" causes confusion. The intent of the sentence should be more clearly stated. It is assumed it means the concentration in the fully processed, finished device.
13	9	10	Eliminate the requirement for describing the manufacturing process.	This can be proprietary information. It is inconsistent with the information required in a 510(k) submission.

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No.	Page No.	Line(s) No.	Change	Rationale
14	9	16, 17	Provide examples or further clarify.	The guidance indicates that the manufacturer should provide supporting “data” to demonstrate how the antimicrobial agent is intended to exert its effect. What kind of data is expected? If the agent is intended to be released from the device then a zone of inhibition is expected and zone of inhibition testing can often be conducted. Other than this type of data, what information is expected? What testing would be expected if the effect is at the surface of the device, i.e. to prevent colonization?
15	10	1	Clarify whether the release kinetics method should simulate conditions expected with clinical use (<i>in vitro</i> vs. <i>in vivo</i> testing). What correlation may be required between the two types of testing?	Routine tests establishing device elution characteristics, initially and over time, may not need to simulate clinical use to be valuable benchmarks.
16	10	2, 3	Add “in or” before “on the device.”	Not all agents are limited to the surface of the device.
17	10	6-12	Eliminate or make optional the requirement to provide information on the distribution and rates of accumulation of the antimicrobial agent from the combination device into tissue or body sites.	The feasibility of measuring the distribution and accumulation of the antimicrobials is dependent upon the amount and duration of the elution of the antimicrobial agent. For a device for which the antimicrobial elution is rapid and/or the amount of antimicrobial eluted is small, the local concentration of the antimicrobial and the amount of tissue affected may be quite small. Due to sampling difficulties and assay

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				<p>sensitivity, this type of data may be technically quite difficult to generate. Unless the intended use for the antimicrobial is specifically to treat or prevent infection, it should not be necessary to measure the accumulation of the microbial agent in the tissues.</p> <p>For antimicrobial devices with the claim of inhibition of colonization, the effect of the antimicrobial on the adjacent tissue (local toxicity) should be addressed by implantation studies with histopathologic assessment of the tissue reaction. For devices that are not claiming to effect a local concentration that constitutes a therapeutic effect, the measurement of the distribution and rates of accumulation of the antimicrobial agent in the tissues constitutes an undue burden.</p> <p>For antimicrobial devices that are intended to treat or prevent infection, the demonstration of sufficient concentration in the target tissues to be efficacious should be more feasible and would be data supportive to the claims.</p>
18	10	7	Clarify if potential tissue accumulation is necessary for implantable devices <u>only</u> .	
19	10	17	Add "mass, or volume" after surface area.	Allows the inclusion of devices where the agent is incorporated in different means other than surface application.

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No.	Page No.	Line(s) No.	Change	Rationale
20	11	18, 19	Add the following: We also recommend you include data demonstrating that the sterilization process does not adversely affect the antimicrobial efficacy of the finished device.	Current wording states that “We also recommend you include data demonstrating that the sterilization process does not adversely affect the activity of the antimicrobial agent.” Many sterilization processes will have some level of adverse effect on the activity of many drugs. However, a modest decrease in drug activity may not affect the efficacy of the finished device.
21	11	21-25	State requirements for shelf-life and stability under a different section of the guidance.	Shelf-life and stability are not related to sterilization per se. Shelf-life and stability must be determined for the fully processed device.
22	11	38-40	This formation appears to be contrary to usual FDA requirements for biocompatibility testing.	Regardless of the “sameness” of materials, manufacturing processes are different, therefore, FDA requires that biocompatibility testing be done on finished devices. Companies may use different equipment, manufacturing materials (mold releases, etc.) and process parameters.
23	12	36, 37	Do not arbitrarily limit the number of passages for clinical isolates. Base it on the stability of phenotypic, and in some instances genotypic characteristics	Limitation to “1-2 passages of the original isolation” can create an unworkable restriction in maintaining a clinical isolate. Allow an option to demonstrate phenotypic and, as appropriate, genotypic stability.
24	13	24-27	Clarify that clinical data may be based on literature or other sources of information.	Existing clinical data may be adequate to support indications for use.

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No.	Page No.	Line(s) No.	Change	Rationale
25	14	19, 20	Clarify how concentration of the antimicrobial agent can be listed for devices where different sizes/models have a range of agent concentrations. Can a range or target level, or maximum amount of antimicrobial agent be listed?	
26	14	19-22	If there is no claim of therapeutic benefit/effect for the patient, are these necessary/pertinent?	
27	14	29	Add "Known" contraindications.	Preclude device manufacturer from having to conduct testing and limit it to information that can be obtained from literature or antimicrobial product data.
28	14	34-36	Remove pharmacology, toxicology, metabolism, and excretion from labeling requirements OR provide guidance on when this information is required.	Pharmacology, toxicology, metabolism and excretion information are not relevant to localized therapies. If the drug has been previously cleared, how much information needs to be provided? This information is not currently provided in antibiotic loaded bone cements.
29	15	2-7	Make it clear that the requirement for the disclaimer applies <u>only</u> to devices for which an indication for use to reduce or inhibit microbial colonization is stated.	Disclaimer does not apply to devices not indicated for use to reduce or inhibit microbial colonization on a medical device.