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October 12, 2007

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

Re: Docket No. 2007D-0201; Comments on the Draft Guidance for Industry and FDA Staff Premarket Notification [510(k)] Submissions for Medical Devices that Include Antimicrobial Agents.

Dear Sir or Madam:

Enturia, Inc submits these comments regarding FDA's Draft Guidance for Industry: Premarket Notification [510(k)] Submissions for Medical Devices that Include Antimicrobial Agents. The Draft Guidance states that FDA is aware that the use of any antimicrobial agent, including its use in or on a device, creates an exposure that may result in the emergence of resistance to the antimicrobial agent in the exposed microbial populations. Antimicrobial resistance is an increasing and serious clinical problem. The guidance is prepared to assist in preparing premarket notification submissions [510(k)s] for medical devices that include antimicrobial agents. We ask to have the below stated comments considered prior to final issue of the Guidance.

I. Overview:

The guidance will require testing of predicate devices as well as the submission devices. Predicate devices have already received authorization to market and should not require additional testing. This is not a least burdensome approach and may impede the introduction of additional devices based on cost-justification. The unintended response from industry may be to introduce devices without antimicrobial agents which subsequently increase patient risk to associated infections.

II. Background: The Development of Bacterial Resistance

The assumption that bacterial resistance will result from exposure to an antimicrobial is not always true. Bacterial resistance can be a non-nucleic modification due to environment. This type modification is not always a permanent adaptation. Specifically on page 2, lines 22-27 our comment is: No consideration is given to the "mode of action" of the microbial agent. Certain classes of chemicals utilize physical rupture of the cellular membrane to kill a microbe, rather than disruption of the reproductive cycle of the bacteria. Mutation of the species is much less likely to occur from this mechanism.

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### III. The Scope of the Draft Guidance Seems Too Broad

The Guidance does not seem to consider the huge variation in devices that may include antimicrobial agents. It no longer considers the current device classifications, nor the time of use of the device (a topical application of less than 24 hours versus permanent contact), monograph qualifications or customization based on design/risk analysis in the "modified" category. The Guidance is mainly applicable to Class II devices but may include Class I devices simply because they contain antimicrobial agents.

### IV. The Definitions for Comparative Devices

This Guidance is deviating from established descriptions of predicate and new devices by introducing "same" and "modified". The criteria for "same" can be easily interpreted as "identical". Our comment is to refine the definitions used in the guidance and to substitute existing terms to maintain consistency throughout the center. Further, Section IV of the Guidance does not lead to clarification nor does it assist in the preparation of premarket notification submissions. In Section IV, page 4, lines 7-14, the statement eliminates any qualification for a 510(k) exemption by defining the addition of an antimicrobial as a "significant modification". There are currently dressings with antimicrobials that are classified as exempt and equivalent products should also be allowed this exemption. Further, in lines 22 -27, the definition of "same" would inhibit improvements within the area of concentration and application by requiring a new submission rather than regarding this as a continuous improvement of the manufacturing process. We request the use of the term "equivalent" and allow more latitude in comparison to the predicate. We also request the elimination of the phrase "with the same agent" after the words predicate device located in Table 1 on page 6, under column "SAME" and row "Descriptive Characterization of the Agent".

### V. Release of Antimicrobial Agents

The guidance expects all antimicrobial agents on a device to have release kinetics. The functional application of agent release is restricted to the time of expected contact and as such may not exist. Devices currently exist with antimicrobial agents designed to remain on the device to prevent biofilm or bacterial colony formation on the device. These devices would not exhibit release kinetics. Therefore, on page 6 in Table 1, under column "SAME" and row "Descriptive Characterization of the Agent", we request the elimination of the bullet "mechanism by which the agent is released from the device" and the removal of "release kinetics" under column "Modified".

Our further comment on Table 1, under the column "Modified", in the row "Characterization of the Product" regarding the clinical studies and footnote\*\*\* vague language is the interpretation to require extensive testing of the predicate device in addition to the submitted device. This is too burdensome a requirement considering the predicate is an already marketed device and does not affect the

safety or efficacy of the submitted device. We request clarification and removal of any requirement to test the predicate device.

#### VI. Indications for Use

The identification of the target pathogens to the genus and species level is impractical for a general antimicrobial such as Chlorhexidine Gluconate (CHG), Neosporin, alcohol, etc. that meet the TFM for Topical Antimicrobial Drug Products for Over-the-Counter Human Use. Furthermore, including such target pathogens on a label as suggested on line 16, page 14 becomes burdensome and excessive.

#### VII. Rationale for Adding the Agent to the Device

This section is vague and burdensome. The emergence of resistant microbial strains is not accurately predictable. The rationale of eliminating one case of infection could be justification for the inclusion of an antimicrobial. Does the agency wish to make decisions on how many people will benefit before it allows the addition of an antimicrobial agent to a device? The anticipated benefit of the antimicrobial agent is subjective and cannot be confirmed until the product is in the marketplace. The marketplace represents the final determination of benefit.

#### VIII. Characterization of the Antimicrobial Agent

On page 8, lines 5-8 and 13-18, the manufacturing process of adding, coating or otherwise incorporating the antimicrobial into the device is not a safety or effectiveness issue, and should be deleted. Manufacturers following QSR and meeting final product release specifications should cover this area. Agent release should not be assumed, and leachables are traditionally tested on devices.

#### IX. Identity and Formulation

Antimicrobial concentration of all constituents prior and after application is burdensome and impractical. If the antimicrobial was solvent deposited, electrodeposited, or spray coated, some constituents would not be present after application. The concern should not be in the application efficiency or the residual solutions, but in the active on the device. Raw material specifications and the device final release specification should satisfy this concern.

#### X. Mechanism of Action

On page 9, section D, debate can be initiated delineating between site action and local action and either may contribute in determining efficacy and neither may affect safety. However, it is significant to determine if the antimicrobial agent becomes systemic, thereby initiating a new risk analysis. We recommend a clarification of this section by selection of a "systemic" or "non-systemic" mechanism of action.

#### XI. Release Kinetics of the Antimicrobial Agent

The requirement of the manufacturer to demonstrate the antimicrobial agent is permanently bound to the device is excessive if the device has a limited or prolonged contact with tissue. The requirement should be limited to the time of use/contact of the device. The reference to elution from an implantable medical device should be removed. The device, unless temporary, does not qualify for premarket notification 510(k) but would require a premarket authorization.

#### XII. Minimum Effective Concentration

Given that one of the primary goals of this guidance is to reduce the emergence of microbial resistance, the use of language like "minimum effective concentration" conveys the wrong message about dosage. We recommend this language be changed to read "maximum tolerated dosage" which better conveys the appropriate objective of antimicrobial therapy: to kill the infecting bacteria before they can develop resistance.

#### XIII. Biocompatibility Testing of the Finished Final Product

The nature of antimicrobial agents may invalidate the use of many of the ISO-10993 test methods especially primary eye irritation testing and sensitization testing. The expectation that the standardized test will fail should allow the exclusion of that test without prejudice in the application. Appropriate testing will be part of the safety testing as determined by a risk analysis.

#### XIV. Performance Testing

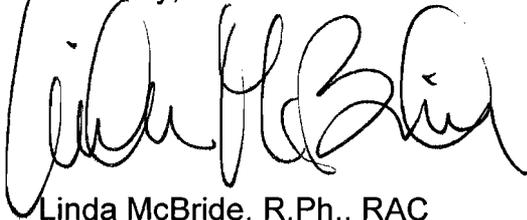
When bench testing a device, it is typical to precondition a device with serum, rather than "body fluid". It is also typical to use a Modified Robbin's Device for a dynamic test environment. It is our comment that the test for any effect of elution be conducted over time of usage rather than over an undefined time. The guidance for clinical studies is vague and elusive. To be helpful, this guidance must describe the specific circumstances that require clinical studies.

#### XV. Labeling

The amount of information detailed in this section cannot physically be placed on a label along with directions for use. This is a massive labeling requirement with particular objection to lines 16 – 22 and lines 29 – 36 on page 14. This information is often of a proprietary and confidential nature and should not be required on a public label. The disclaimer indicates an option to forego clinical studies and proceed with the 510(k). Would the claim of "barrier to infection" also be allowed under this disclaimer?

Enturia, Inc. appreciates the opportunity to comment on this Draft Guidance and presents these comments toward a goal of clarification and improvement. If you have any questions associated with these comments, please feel free to contact Arlen Johnson at (913)345-3570 or myself at (913)345-3562.

Sincerely,

A handwritten signature in black ink, appearing to read 'Linda McBride', written in a cursive style.

Linda McBride, R.Ph., RAC  
Senior Director, Regulatory Affairs