

Draft Guidance for Industry and FDA Staff

Premarket Notification [510(k)] Submissions for Medical Devices that Include Antimicrobial Agents

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For questions regarding this document, contact Sheila Murphey, M.D. or Michelle Rios at 240-276-3747, or via email at sheila.murphey@fda.hhs.gov or michelle.rios@fda.hhs.gov, respectively.



**U.S. Department of Health and
Human Services
Food and Drug
Administration**

Center for Devices and Radiological Health

Office of Device Evaluation

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Preface

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This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. Introduction

In recent years there has been increased interest in adding antimicrobial agents to medical devices for a specific or limited indication for use, such as reduction or prevention of a device-related infection, or reduction or inhibition of colonization of a medical device. FDA is receiving an increasing number of 510(k) submissions for medical devices that include antimicrobial agents. FDA has developed this guidance document to assist industry in preparing premarket notification submissions (510(k)s) for medical devices that include antimicrobial agents.¹

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

The Least Burdensome Approach

This draft guidance document reflects our careful review of what we believe are the relevant issues related to medical devices that include an antimicrobial agent and what we believe would be the least burdensome way of addressing these issues. If you have

¹ The addition of an antimicrobial agent to a device creates a combination product if the antimicrobial component meets the definition of a drug in section 201(g) of the Act (see 21 CFR 3.2(e).) For additional information on combination product jurisdiction, please refer to the FDA Office of Combination Products (<http://www.fda.gov/oc/combination>).

1 comments on whether there is a less burdensome approach, however, please submit your
2 comments as indicated on the cover of this document.

3 4 **II. Background**

5 Antimicrobial agents are substances that kill or inhibit the growth of microorganisms. In
6 certain instances when antimicrobial agents are included on a device, they will be considered
7 drugs² and the resulting device that includes the antimicrobial drug will be considered a
8 combination product as defined in 21 CFR 3.2(e). In many instances in which the
9 antimicrobial acts outside the body, such as antimicrobial sterile drapes and gloves used in
10 patient procedures, FDA does not treat the antimicrobial as a drug. FDA has regulated such
11 products as devices rather than combination products.

12
13 The Center for Devices and Radiological Health (CDRH) regulates devices containing
14 antimicrobial agents and combination products containing antimicrobial drugs when the
15 primary mode of action³ is that of a device. Such devices and combination products are
16 regulated by CDRH under the device provisions of the Federal Food, Drug and Cosmetic
17 Act.⁴ In the guidance that follows, the terms “antimicrobial agent(s)” will refer to any
18 antimicrobial agents, including those that are considered to be drugs. The term “device” in
19 this guidance will refer both to devices containing antimicrobial agents and combination
20 device/drug products containing antimicrobial drugs.

21
22 FDA is aware that the use of any antimicrobial agent, including its use in or on a device,
23 creates an exposure that may result in the emergence of resistance to the antimicrobial agent
24 in the exposed microbial populations. Antimicrobial resistance is an increasing and serious
25 clinical problem. Further, the antimicrobial spectrum of sensitivity changes over time. FDA
26 believes that the potential clinical benefit of the use of an antimicrobial agent, including its
27 use on a medical device, should outweigh the associated risk. FDA will compare the risks

² Drugs are defined in Section 201(g) of the Federal Food, Drug, and Cosmetic Act (the act) as “(A) articles recognized in the official United States Pharmacopeia, official Homeopathic Pharmacopeia of the United States, or official National Formulary, or any supplement to any of them; and (B) articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals; and (C) articles (other than food) intended to affect the structure or any function of the body of man or other animals; and (D) articles intended for use as a component of any articles specified in clause (A), (B), or (C)” (21 USC 321(g)).

³ The primary mode of action of a combination product is the single mode of action (i.e., drug, device, biological product) that provides the most important therapeutic action of the combination product. 21 C.F.R. 3.2(m). This is also the mode of action expected to make the greatest contribution to the overall therapeutic effect of the combination product. Under section 503(g) of the Act, the primary mode of action of a combination product determines the agency component responsible for premarket review of the product. In the context of this guidance, an antimicrobial has a drug mode of action if it meets the definition of drug contained in section 201(g)(1) of the act and it does not have a biological product or device mode of action. Further, in some instances, such as antimicrobial swabs, where the primary mode of action is attributable to the antimicrobial component of an antimicrobial-device combination product, the product would be assigned to CDER.

⁴ See 21 C.F.R. § 3.4.

and benefits of a device containing an antimicrobial agent to those of its predicate in evaluating substantial equivalence.⁵

III. Scope

This guidance is intended for devices containing antimicrobial agents and combination products containing antimicrobial drugs when the primary mode of action is that of a device. This document provides FDA's recommendations for information that should be submitted in a 510(k) for a medical device or a combination product containing an antimicrobial agent or multiple antimicrobial agents.

A. Exclusions

The products listed below are not within the scope of this guidance:

- drug delivery devices, whose primary intended use is to deliver an antimicrobial drug;
- germicides or sterilants used to reprocess reusable critical and semi-critical devices;⁶
- germicides or sterilants used for pre-cleaning or decontamination of critical or semi-critical surfaces, when the label states that this is done before terminal sterilization or disinfection;
- combination products where the drug component is a new chemical entity (NCE).⁷

B. Additional Information

FDA recommends the use of this guidance document as a supplement to other CDRH guidance, in particular, any device-specific guidance relevant to your device.

Manufacturers should also refer to 21 CFR 807.87, the guidance, **Format for Traditional and Abbreviated 510(k)s**⁸, and the section of CDRH's Device Advice, **How to Prepare**

⁵ Section 513(a)(2) of the Act provides that the safety and effectiveness of a device are to be determined "weighing any probable benefit to health from the use of the device against any probable risk of injury or illness from such use." Thus, a determination of safety and effectiveness of a device and its predicate involves an assessment of their risks and benefits.

⁶ The terms "critical device" and "semi-critical device" generally refer to devices that during use contact normally sterile tissue or body spaces (critical), and those that during use contact mucous membranes or non-intact skin (semi-critical).

⁷ A new chemical entity (NCE) is a drug that contains no active moiety that has been approved by FDA in any other application submitted under section 505(b) of the [Federal Food, Drug, and Cosmetic Act](#). An active moiety means the molecule or ion, excluding those appended portions of the molecule that cause the drug to be an ester, salt (including a salt with hydrogen or coordination bonds), or other noncovalent derivative (such as a complex, chelate, or clathrate) of the molecule, responsible for the physiological or pharmacological action of the drug substance. *See* 21 C.F.R. § 314.108.

⁸ <http://www.fda.gov/cdrh/ode/guidance/1567.html>

a **510(k) Submission**⁹, for additional information about preparing 510(k)s. Manufacturers can also obtain information about combination products from the FDA Office of Combination Products at (301) 427-1934 or <http://www.fda.gov/oc/combination/>.

IV. Recommendations for Devices that Include Antimicrobial Agents

FDA believes that the addition of an antimicrobial agent to a legally marketed medical device generally represents a significant modification that, in accordance with 21 CFR 807.87(g), requires a new 510(k) submission.¹⁰ We also believe the addition of an antimicrobial agent to a legally marketed Class I or Class II device that is exempt from 510(k) generally exceeds the limitations of exemption described in the general provisions of the applicable Part (*see* the .9 regulations of 21 C.F.R. Parts 862-892). When a modification exceeds the limitations of exemption, the modified device is not exempt from the 510(k) requirements.

Our recommendations for a medical device that includes an antimicrobial agent depend, in part, on whether the device has a legally marketed predicate (21 CFR 807.92(a)(3)) with the same device design and the same antimicrobial agent for the same indication for use.

FDA considers a device with an antimicrobial agent to be the “same” for the purposes of this guidance if:

1. the antimicrobial agent, when compared to the predicate, has the same:
 - identity, formulation, and concentration
 - method of application to the device (such as attachment, incorporation, or coating)
 - mechanism by which the agent is released from the device; and
2. the device that includes the antimicrobial agent has the same indication for use as compared to the predicate, including the same anatomical site at which the product is to be used; and
3. the device has the same design characteristics (such as material, geometry, functions) as the predicate.

FDA considers a device that includes an antimicrobial agent, but does not meet the above criteria, to be “modified” for the purposes of this guidance. A “modified” device in this context is one that, for example, has a different polymer formulation, a different means by which the antimicrobial is bound on or in the device, or a change to the antimicrobial agent.

⁹ <http://www.fda.gov/cdrh/devadvice/314.html>

¹⁰ In some cases, we may find your modified device raises new types of safety and effectiveness questions. If it does, your modified device will be found not substantially equivalent (NSE). It will then be in Class III and subject to the premarket approval (PMA) requirements of the act (section 513(a) of the act, 21 U.S.C. 360c(a)).

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1 When the device is designated “same” for the purposes of this guidance, the information
2 required to support substantial equivalence will generally be less than what is required for a
3 “modified” device. When the device is “modified” (as described in this guidance) FDA
4 recommends manufacturers provide additional information about the properties of the agent,
5 the device, and the device with the agent included. Table 1 summarizes the information and
6 testing results FDA recommends you submit for devices that include antimicrobial agents.
7

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Table 1. Recommendations for Devices that include Antimicrobial Agents

	"SAME"	"MODIFIED"
Product Description	<p>INDICATION FOR USE (same as predicate – including anatomical site)</p> <p>RATIONALE for adding the antimicrobial agent to the device</p> <p>DETAILED DESCRIPTION OF THE DEVICE</p>	<p>INDICATION FOR USE (same or different from predicate)</p> <p>RATIONALE for adding the antimicrobial agent to the device</p> <p>DETAILED DESCRIPTION OF THE DEVICE</p>
Descriptive Characterization of the Agent	<p>DESCRIPTIVE COMPARISON to a predicate device with the same agent, demonstrating that the antimicrobial agent is the same by comparing the following aspects of the proposed device and the predicate:</p> <ul style="list-style-type: none"> identity, formulation, and concentration method of application to the device mechanism by which the agent is released from the device. 	<p>DETAILED DESCRIPTION and PRE-CLINICAL TESTING of the antimicrobial agent:</p> <ul style="list-style-type: none"> identity and formulation concentration method of application to device mechanism of action antimicrobial activity spectrum (profile) release kinetics minimum effective concentration (MEC) toxicity of agent
Characterization of the Product†	<p>DESCRIPTIVE COMPARISON to predicate††</p> <p>STERILIZATION (if provided as sterile)</p> <p>BIOCOMPATIBILITY</p> <p>PERFORMANCE TESTING of the device††</p>	<p>DESCRIPTIVE COMPARISON to predicate</p> <p>STERILIZATION (if provided as sterile)</p> <p>BIOCOMPATIBILITY</p> <p>PERFORMANCE TESTING that demonstrates that the product is as safe and effective as the predicate including:</p> <ul style="list-style-type: none"> in vitro testing animal testing clinical studies***

†FDA recommends that you use the final finished product in all testing.

††Generally, FDA recommends submitting the same descriptive comparison and performance testing for a device designated as “same” for the purposes of this guidance as was performed to establish the predicate. FDA may, however, recommend additional information, depending on the features and characteristics of your device.

***The need for clinical data and specific clinical study design recommendations will depend on the proposed indication for use, device design, the identity of the antimicrobial agent, and any other potential safety and effectiveness considerations.

The following three sections explain the terms used in Table 1 and describe in detail the information we recommend you submit.

V. Device Description

FDA believes that the addition of antimicrobial agents to medical devices has the potential to increase the risk of antimicrobial resistance. Therefore, FDA discourages the indiscriminate use of antimicrobial agents on devices and recommends that the clinical benefit of the added antimicrobial agent when compared to the predicate should outweigh the associated risk. In 510(k)s for all devices that include antimicrobial agents, the manufacturer should state the indications for use and rationale for adding the antimicrobial, as described below.

A. Indications for Use

The 510(k) should state the indication for use of the device that includes an antimicrobial agent. FDA believes the following indications may be appropriate for devices that include an antimicrobial agent:

- reduces or prevents device-related infections
- reduces or inhibits microbial colonization on a medical device.

The indication for use statement for the device with an added antimicrobial agent should also include an identification of the target pathogens to the genus and species level. Protocols for studies to support certain indications for use for devices with added antimicrobial agents, such as claims for removing or preventing biofilm build up, should be discussed with FDA in advance.

B. Rationale for Adding the Agent to the Device

The 510(k) should include a discussion of the underlying scientific or clinical rationale (or both, as applicable) for adding the specific antimicrobial agent to the device. This should include the identification of the target bacterial species (genus and subtype). In addition, your rationale should compare the potential impact of the antimicrobial agent on the emergence of resistant microbial strains to the anticipated benefit of the antimicrobial agent on the device.

C. Detailed Description of the Device with the Antimicrobial Agent Added

The description of the device with the added antimicrobial agent should be detailed and include:

- information about the material and the specifications used to manufacture the device with the antimicrobial agent, including any additives, plasticizers, or other compounds;
- a list of all device materials, identifying the materials that are coated or combined with the antimicrobial agent and those that are patient contacting; and
- any effect on the specifications or performance of the device related to the addition of the antimicrobial agent. This could include material or surface changes, or changes to device integrity, stability, and mechanical durability.

VI. Characterization of the Antimicrobial Agent

For a device designated the “same” for the purposes of this guidance, FDA recommends manufacturers provide a descriptive comparison to a predicate device with the same agent. Manufacturers should demonstrate that the antimicrobial agent is the same by comparing the:

- identity and formulation of the antimicrobial agent
- concentration of the antimicrobial agent on the device
- method used to apply the antimicrobial agent to the device
- mechanism by which the agent is released.

For a device designated “modified” for the purpose of this guidance, FDA recommends manufacturers provide detailed information and pre-clinical testing to demonstrate substantial equivalence. Such information and testing should include the:

- identity and formulation of the agent
- concentration of the antimicrobial agent on the device
- method used to apply the antimicrobial agent to the device
- mechanism of action of the agent
- antimicrobial activity spectrum of the agent
- release kinetics of the agent from the device over time
- minimum effective concentration (MEC)
- toxicity of the agent.

Each of these topics is discussed below.

A manufacturer may be able to limit the amount of information needed to show substantial equivalence for a device that includes an antimicrobial that has been approved in a new drug application (NDA) or over the counter (OTC) monograph by referring to the NDA or OTC monograph. A manufacturer may only rely on proprietary data if the manufacturer has obtained a right of reference from the rights holder. These references may limit the amount of information needed to be generated by the manufacturer for characterization of the antimicrobial agent. Manufacturers should identify any differences between the approved drug product (NDA or OTC) and the antimicrobial agent that has been added to the medical device. These may include differences in the intended use, dosage, anatomical site where the agent is used, formulation and concentration. The manufacturer should evaluate the impact of these differences and determine whether additional information or data are needed.

A. Identity and Formulation

The manufacturer should identify the antimicrobial agent and describe its formulation, including:

- any accompanying polymer substrate or additives
- the purpose of the accompanying substances

- the formulation and concentration of all its constituents prior to and after application to the device.

B. Concentration

Manufacturers should describe the starting concentration of the antimicrobial agent in or on the device and the method used to calculate its concentration for each model and size of the finished device after any applicable terminal processing step.

C. Method of Application to the Device

Manufacturers should describe the manufacturing process for adding the antimicrobial agent to the medical device. The description should include the specifications, such as concentration, thickness (of coatings), and how the antimicrobial is incorporated or bound to the device.

D. Mechanism of Action

Manufacturers should describe the mechanism of action and provide supporting data that demonstrate how the antimicrobial agent is intended to exert its effect. For example, manufacturers should indicate whether the antimicrobial agent effect is achieved at the site of device attachment or by acting locally due to the release of the agent from the device.

E. Antimicrobial Activity Spectrum (Profile)

Manufacturers should provide information on the antimicrobial activity spectrum (i.e., profile of microbicidal activities) of the added antimicrobial agent. Recent literature references may be sufficient for this purpose, if the literature cited is clearly relevant to the subject agent and the target pathogens. Alternatively, if the information of the activity spectrum is provided in an NDA, a monograph, or a drug master file, the manufacturer may reference these documents in lieu of providing the recommended information, provided the manufacturer has obtained a valid right of reference for any proprietary information.

The antimicrobial spectrum of activity of the antimicrobial agent may be determined by standardized methods such as those developed by the Clinical and Laboratory Standards Institute [CLSI (1,2)].^{11,12}

F. Release Kinetics of the Antimicrobial Agent

The release mechanism of the antimicrobial agent should be fully characterized and the release kinetics from the device should be demonstrated using a method having an adequate level of detection. The elution method should be validated and the limits of

¹¹ CLSI. Performance Standards for Antimicrobial Disk Susceptibility Test; Approved Standard -9th ed. NCCLS document M2-A9. CLSI, 940 West Valley Rd., Ste 1400, Wayne, PA 19087-1898, 2006.

¹² CLSI. Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically; Approved Standard – 7th ed. CLSI document M7-A7 (ISBN 1-56238-394-9). NCCLS, 940 West Valley Rd. Ste 1400, Wayne, PA 19087-1898, 2006.”

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1 detection should be provided. Release kinetics information should include the initial
2 concentration of the antimicrobial agent on the device and any changes in the
3 concentration on the device over time.
4

5 If the antimicrobial agent does not elute from the device, the manufacturer should
6 demonstrate that the antimicrobial agent is permanently bound to the medical device. If
7 the antimicrobial agent elutes from an implantable medical device, then the manufacturer
8 should provide information on the distribution and rates of accumulation of the
9 antimicrobial agent in tissue or body sites. If the antimicrobial agent's distribution
10 kinetics information is provided in an NDA, a monograph or a drug master file and is
11 available, the manufacturer may reference these documents in lieu of providing the
12 antimicrobial agent's kinetics information.
13

G. Minimum Effective Concentration (MEC)

15 Manufacturers should identify the minimum effective concentration of the antimicrobial
16 agent in or on the device that achieves the stated purpose. The minimum effective
17 concentration should be stated as concentration per surface area and total concentration
18 per device. Manufacturers should conduct testing to measure the MEC under conditions
19 that are consistent with clinical use of the device. The 510(k) should include a
20 description of these methods and conditions.
21

H. Toxicity

23 Manufacturers should assess the toxicity of the antimicrobial agent, active metabolites,
24 and degradation products in the body. Manufacturers should also include any literature
25 that addresses the toxicity of the antimicrobial agent and its active metabolites and
26 degradation products. In addition, manufacturers should provide information on residues
27 or substances that can leach out from the medical device and describe how to mitigate
28 any risk posed to the user by those residues.

29 Data from pre-clinical or clinical studies may be appropriate to fully characterize the
30 toxicity of the antimicrobial agent. Toxicity testing should identify any adverse effects of
31 the added antimicrobial agent, such as agent-dependent adverse reaction
32 (allergic/immune responses or other toxicity), or agent interactions with device materials.
33 The 510(k) should include all study protocols and a description of the test methods used.
34

VII. Characterization of the Device with an Added Antimicrobial Agent

37 The extent of information and testing appropriate to characterize a device depends on
38 whether the device-agent is designated "same" or "modified" for the purposes of this
39 guidance. FDA's recommendations for the products addressed in this guidance are described
40 in detail below. For additional information about characterization of the device,
41 manufacturers should refer to device-specific guidance, if available for that device type, or
42 contact the device review branch.

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A. Descriptive Comparison

Generally, for a device that includes an antimicrobial, whether the “same” or “modified,” FDA recommends you submit the same type of descriptive comparison with a predicate as you submit for a device that does not include an antimicrobial.

If the device is designated “same” for the purposes of this guidance, a descriptive comparison that includes the aspects, features, and characteristics of the device relevant to substantial equivalence for that device type is generally adequate. FDA may, however, recommend submitting additional information or testing depending on the design, technology, indications, or other aspects of a particular device if the descriptive characteristics alone are not sufficient.

B. Sterilization of the Final Finished Product

For devices sold as sterile, we recommend that you follow the guidance, **Updated 510(k) Sterility Review Guidance K90-1**.¹³

We also recommend you include data demonstrating that the sterilization process does not adversely affect the activity of the antimicrobial agent.

For a submission that identifies a shelf life for the device, the shelf life should be supported by appropriate bench testing. We recommend you provide information on the stability of the antimicrobial agent over the shelf-life of the device after any applicable terminal processing step, such as sterilization. We also recommend you use a release test to evaluate elution of the antimicrobial agent in establishing the stability and shelf-life.

C. Biocompatibility Testing of the Final Finished Product

If your device contains components that come into direct or indirect contact with patients, you should evaluate the biocompatibility of the patient-contacting materials. All testing should be performed on the final finished product with the added antimicrobial agent.

Please refer to the guidance document titled **Use of International Standard ISO-10993, and Biological Evaluation of Medical Devices Part 1: Evaluation and Testing**.¹⁴ You should select biocompatibility tests for the duration and type of contact appropriate to your device design and submit the pass/fail criteria or in some cases, a summary of the results.

If identical materials are used in a predicate with the same added antimicrobial, type and duration of patient contact, you may identify the predicate in lieu of performing biocompatibility testing and state that your device is comprised of identical materials processed by identical manufacturing methods. This is most appropriate if you are the manufacturer of the predicate and you have complete documentation with respect to the manufacturing methods and materials employed.

¹³ www.fda.gov/cdrh/ode/guidance/361.html

¹⁴ www.fda.gov/cdrh/g951.html

D. Performance Testing

The indication for use of the antimicrobial agent, as it relates to the device, determines the extent of additional testing the manufacturer should conduct. For devices designated "modified" for the purposes of this guidance, FDA recommends manufacturers submit *in vitro*, animal, and clinical data, as appropriate, to demonstrate that the device with the antimicrobial agent is as safe and effective as the predicate.¹⁵ Our recommendations for these studies are described in detail below.

Generally, the performance testing FDA recommends for that device type without an antimicrobial agent is adequate for a device designated "same" for the purposes of this guidance. FDA may, however, recommend you submit additional testing, depending on the design, technology, indications, or other aspects of your device.

For additional information about performance testing, manufacturers should refer to device-specific guidance, if available for that device type, or contact the device review branch. For the devices addressed in this guidance, FDA recommends manufacturers perform all testing on the finished device, i.e., the device with the antimicrobial after packaging and any applicable terminal processing step, such as sterilization. The 510(k) should include the performance specifications for the final finished device.

1. Bench Testing

For a "modified" device with an added antimicrobial agent, FDA recommends that manufacturers conduct *in vitro* studies to demonstrate the antimicrobial effectiveness of the agent on the device for the stated indications for use. *In vitro* studies should incorporate exposure conditions that simulate clinical use of the device. Depending on the device, these conditions may include:

- temperature
- preconditioning of the device with body fluid
- dynamic (rather than static) environment
- contact time with the body
- contact time with microorganisms.

Manufacturers should assess antimicrobial effectiveness with representatives of the normal flora and relevant clinical isolates to show the spectrum and activity of the antimicrobial agent on the medical device. FDA recommends the clinical isolates used in the studies be within 1–2 passages of the original isolation. The study should include a comparison of the "modified" device with a control device. The control device should be identical to the "modified" device without the antimicrobial agent.

The study should also establish the relationship between the antimicrobial effectiveness and the effective concentration of the antimicrobial agent in or on the

¹⁵ See also section 513(i)(1)(A)(ii)(I) of the act.

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device. If the antimicrobial agent elutes from the device over time, then the study should be designed to test the effect of such elution over time on the antimicrobial effectiveness.

The submission should include a description of all test methods, including:

- inoculation and recovery techniques for the test organisms
- use of neutralizers (to neutralize any carry-over of antimicrobial agent in the recovery procedure)
- recovery media
- incubation temperature
- incubation time.

In addition to studies of antimicrobial effectiveness, we recommend you conduct bench studies to assess the antimicrobial agent's effect, if any, on the specifications or performance of the device. This should include an assessment of material or surface changes, and changes to device integrity, stability, and mechanical durability.

2. Animal Studies

Animal studies may be appropriate to evaluate the effectiveness of the device with an added antimicrobial agent for its indication for use. We recommend that you contact FDA for further guidance (see title page for contact information).

3. Clinical Studies

FDA believes the indication for use, "reduce or prevent device-related infections" should be supported by clinical data. Additionally, in some circumstances, FDA may recommend clinical data to address safety or effectiveness concerns that cannot be satisfactorily addressed with *in vitro* bench testing or animal studies.

Depending on the indications for use, the nature of the antimicrobial agent, and the study protocol, FDA may consider the device a significant risk device, as defined in 21 CFR 812.3(m)(4).¹⁶ If so, the study must be conducted under an approved Investigational Device Exemption (IDE), see 21 CFR Part 812. If the device is considered a non-significant risk device,¹⁶ the study does not require FDA approval of an IDE, but it is subject to the abbreviated requirements of 21 CFR 812.2(b). In either case, sponsors of clinical studies must comply with the regulations governing institutional review boards (21 CFR Part 56) and informed consent (21 CFR Part 50).

The manufacturer should provide the rationale for the use of any surrogate markers as endpoints in clinical studies intended to demonstrate the reduction or prevention of infections by the antimicrobial agent. We believe a sufficient rationale would normally include evidence, reported in peer-reviewed literature, of an established consensus on the use of the subject surrogate markers of infection.

¹⁶ See <http://www.fda.gov/oc/ohrt/irbs/devices.html#risk>

VIII. Labeling

The 510(k) should include labeling in sufficient detail to satisfy the requirements of 21 CFR 807.87(e). The following suggestions are aimed at assisting you in preparing labeling that satisfies the requirements of 21 CFR Part 801.¹⁷

In general, labeling should describe the device, its indications for use, and provide the directions for use. The directions for use should include any warnings, contraindications, and limitations that apply. For labeling recommendations for a specific device type, manufacturers should refer to device-specific guidance, if available, or contact the device review branch.

Labeling should include separate sections for:

- the indication for use of the antimicrobial agent
- chemical name of each antimicrobial agent
- target pathogens (genus and species)
- spectrum of activity of the antimicrobial agent, including how this activity spectrum relates to the types of organisms encountered during typical clinical use
- concentration of the antimicrobial agent on the device and the amount released to or contacting the patient during device use, if applicable
- summary of the safety and effectiveness data for the device with the added antimicrobial agent, including any clinical study results, if applicable.

Labeling should also include warnings about or contraindications to the use of the device, if any, for example:

- the potential for hypersensitivity or allergic reaction to the antimicrobial agent
- contraindications against use of the device in patients with a history of hypersensitivity to the antimicrobial agent
- contraindications for use in the presence of certain drug therapies.

Labeling should also provide information characterizing the antimicrobial agent's:

- chemistry
- pharmacology
- toxicology
- metabolism and excretion information, if applicable.

¹⁷ Although final labeling is not required for 510(k) clearance, final labeling must comply with the requirements of 21 CFR 801 before a medical device is introduced into interstate commerce. In addition, final labeling for prescription medical devices must comply with 21 CFR 801.109. Labeling recommendations in this guidance are consistent with the requirements of Part 801.

Contains Nonbinding Recommendations

Draft - Not for Implementation

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If the indication for use is to reduce or inhibit microbial colonization on a medical device, labeling should contain an appropriate disclaimer. For example:

Reduction in colonization or microbial growth on the device has not been shown to correlate with a reduction in infections in patients. Clinical studies to evaluate reduction in infection have not been performed.

DRAFT