Submission and Review of Sterility Information in Premarket Notification (510(k)) Submissions for Devices Labeled as Sterile

Guidance for Industry and Food and Drug Administration Staff

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This document has been revised on January 8, 2024 to update the lists of the established sterilization methods.

This document supersedes Submission and Review of Sterility Information in Premarket Notification (510(k)) Submissions for Devices Labeled as Sterile issued January 21, 2016, and subsequently updated March 16, 2016 to correct an inadvertent editorial change regarding reporting of endotoxin limits.

For questions about this document regarding CDRH-regulated devices, contact the Sterility Devices Team at OHT4_SterilityDeviceTeam@fda.hhs.gov.

For questions about this document regarding CBER-regulated devices, contact CBER's Office of Communication, Outreach, and Development (OCOD) at 1-800-835-4709 or 240-402-8010.

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U.S. Department of Health and Human Services
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Preface

Public Comment

You may submit electronic comments and suggestions at any time for Agency consideration to http://www.regulations.gov. Submit written comments to the Division of Dockets Management, Food and Drug Administration, 5630 Fishers Lane, Room 1061, (HFA-305), Rockville, MD 20852. Identify all comments with the docket number FDA–2008–D–0611. Comments may not be acted upon by the Agency until the document is next revised or updated.

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Submission and Review of Sterility Information in Premarket Notification (510(k)) Submissions for Devices Labeled as Sterile

Guidance for Industry and Food and Drug Administration Staff

This guidance represents the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff or Office responsible for this guidance as listed on the title page.

I. Introduction

This guidance document updates and clarifies the information regarding sterilization processes that we recommend sponsors include in 510(k)s for devices labeled as sterile. This guidance document also provides details about the pyrogenicity information that we recommend sponsors include in a 510(k) submission. For the current edition of the FDA-recognized standards referenced in this document, see the FDA Recognized Consensus Standards Database.[1] For more information regarding use of consensus standards in regulatory submissions, please refer to the FDA guidance titled "Appropriate Use of Voluntary Consensus Standards in Premarket Submissions for Medical Devices."[2].

In general, FDA's guidance documents 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.

II. Background

In recent years, FDA has received an increasing number of 510(k)s for devices labeled as sterile that use sterilization methods other than the traditionally used methods of steam, dry heat,

[1] Available at https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfStandards/search.cfm
[2] Available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/appropriate-use-voluntary-consensus-standards-premarket-submissions-medical-devices

ethylene oxide (EO), and radiation. FDA has experience with other methods, such as vaporized hydrogen peroxide, ozone and flexible bag systems, and now considers them to be **established** methods. However, we recognize that there may be alterations to the more recently developed methods, as well as original, innovative sterilization technologies, which are being developed and proposed for use in the manufacture of class I and class II devices. FDA considers these to be **novel** methods. (The terms "**established**" and "**novel**" are defined in Section IV below.)

Under section 513(f)(5) of the Federal Food, Drug, and Cosmetic Act (the act), FDA may not withhold 510(k) clearance for failure to comply with any provision of the act unrelated to a substantial equivalence decision, including failure to comply with Good Manufacturing Practice (GMP),[3] unless FDA finds that there is a substantial likelihood that failure to comply with the provision "will potentially present a serious risk to human health." We believe that **novel** sterilization technologies carry a substantial risk of inadequate sterility assurance if not conducted properly. Consequently, compliance with GMP for devices sterilized using these technologies should be closely evaluated. Failure to assure sterility presents a serious risk to human health because of the risk of infection. Therefore, we intend to inspect the manufacturing facility before clearing a 510(k) for a device that is sterilized by a **novel** sterilization process. Inspecting the manufacturing facility for devices sterilized using these sterilization technologies will help ensure the safety and effectiveness of these devices and mitigate the risks to human health.

III. Scope

The scope of this guidance is limited to the review of 510(k)s for devices labeled as sterile that are subject to industrial terminal sterilization processes based on microbial inactivation. Examples of these processes include radiation, steam, EO, and new technology sterilization processes.

Exclusions
The following are excluded from this guidance:

1. Sterilizers that are themselves medical devices subject to 510(k).[4,5]

2. Processes that rely on microbial exclusion, rather than microbial inactivation, are outside the scope of this guidance. Examples of microbial exclusion processes include sterilizing filtration methods and aseptic processing, commonly used in pharmaceutical manufacturing.

3. Processes intended to sterilize medical devices that incorporate materials of animal origin (i.e., human or animal tissues) are outside the scope of this guidance. We recommend

[3] The implementing regulations for GMP requirements, section 520(f) of the Federal Food, Drug, and Cosmetic Act, are referred to as Quality System (QS) requirements (see also 21 CFR Part 820).
[4] Ethylene oxide gas sterilizer, 21 CFR 880.6860, dry-heat sterilizer, 880.6870, and steam sterilizer 880.6880.
[5] See "Guidance on Premarket Notification (510(k)) Submissions for Sterilizers Intended for Use in Health Care Facilities," (available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/guidance-premarket-notification-510k-sterilizers-intended-use-health-care-facilities)

contacting the branch responsible for the review of your device to discuss questions about devices that contain materials of human or animal origin. To assist sponsors in addressing the concerns or issues related to viral contamination, we recommend review of United States Pharmacopeia (USP) <1050>, *Viral Safety Evaluation of Biotechnology products derived from cell lines of human or animal origin*, and related documents.

4. Processes that incorporate the use of liquid chemical sterilants.[6]

5. Processes intended to be used by reprocessors of single-use devices. See "Medical Device User Fee and Modernization Act of 2002, Validation Data in Premarket Notification Submissions (510(k)s) for Reprocessed Single-Use Medical Devices" (available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/medical-device-user-fee-and-modernization-act-2002-validation-data-premarket-notification)

6. Information on the cleaning, disinfecting, and sterilizing of reusable devices that are reprocessed at healthcare facilities (and for single-use devices that are provided non-sterile for further sterilization at healthcare facilities). See "Reprocessing Medical Devices in Health Care Settings: Validation Methods and Labeling" (available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/reprocessing-medical-devices-health-care-settings-validation-methods-and-labeling)

Finally, FDA notes that the sterilization methods used in manufacturing settings are subject to FDA's Quality System (QS) regulation requirements, 21 CFR Part 820.

IV. Methods of Sterilization

FDA considers there to be two categories of sterilization methods currently used to sterilize medical devices in manufacturing settings: **established** and **novel**.[7] These processes are defined below, and examples are provided for each category.

A. Established Sterilization Methods:

1. **Established Category A:** These are methods that have a long history of safe and effective use as demonstrated through multiple sources of information such as ample literature, clearances of 510(k)s or approvals of premarket approval (PMA) applications, and satisfactory QS inspections. For established methods such as dry heat, EO, steam, radiation, and vaporized hydrogen peroxide, there are voluntary

[6] Liquid chemical sterilants/high level disinfectants, 21 CFR 880.6885, and Automated endoscope reprocessors under Endoscope and accessories, 21 CFR 876.1500.

[7] This characterization scheme applies to processing methods used in manufacturing rather than for specific sterilization cycles on FDA-cleared sterilizers intended for use in health care settings. Please note that this categorization can change over time and sponsors are encouraged to contact FDA for updated information.

consensus standards for development, validation, and routine control that are recognized by FDA.[8]

Examples of these Established Category A Sterilization Methods:

- Dry heat
- EO with devices in a fixed, rigid chamber
- Moist heat or steam
- Radiation (e.g., gamma, electron beam)
- Vaporized Hydrogen Peroxide (H_2O_2)[9]

2. **Established Category B:** There are other established methods for which there are no FDA-recognized dedicated consensus standards, but for which published information on development, validation, and routine control is available.

   In cases where FDA has previously evaluated sterilization development and validation data for specific sterilizers using discrete cycle parameters and determined the validation methods to be adequate,[10] we consider these to be **Established** Category B.

   Examples of these Established Category B Sterilization Methods:

   - Ozone (O_3)
   - Flexible bag systems (e.g., EO in a flexible bag system, diffusion method, injection method)

   However, for those cases where the specific process does not appear to have been evaluated by FDA, either because the parameters of an FDA-cleared sterilizer have been altered, or because process validation data have not been evaluated and found to be adequate in previous cleared or approved submissions, we consider these methods to be **novel**.

B. Novel Sterilization Methods:

These are newly developed methods for which there exists little or no published information, no history of comprehensive FDA evaluation of sterilization development and validation data through an FDA-cleared 510(k) or approved PMA for devices sterilized with such methods, and no FDA-recognized dedicated consensus standards on

[8] For more information, please see FDA's database, Recognized Consensus Standards at http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfStandards/search.cfm

[9] We encourage you to contact the review division for your device regarding the appropriate parameters to monitor for parametric release of product loads sterilized with vaporized hydrogen peroxide. For more information, see the Supplementary Information Sheet (SIS) for FDA's recognition of ISO 22441, *Sterilization of health care products - Low temperature vaporized hydrogen peroxide - Requirements for the development, validation and routine control of a sterilization process for medical devices* available at: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfstandards/detail.cfm?standard__identification_no=44295

[10] This evaluation may take place as part of the review of a 510(k) submission for a sterilizer intended for use in a health care facility or as part of a previous clearance of a 510(k), or approval of a premarket approval application (PMA) or Humanitarian Device Exemption (HDE), for a device sterilized using this specific process.

development, validation, and routine control. A **Novel Sterilization Method** is a method that FDA has not reviewed and determined to be adequate to effectively sterilize the device for its intended use.

A sterilization method that uses chemical(s) that have not been previously cleared or approved by FDA as a chemical sterilant or has not been identified in the scientific literature as a chemical sterilant would be considered novel. In addition, a sterilization method that uses a combination of chemicals, and the combination has not been previously cleared or approved by FDA as a sterilant, would be considered novel even if the individual chemicals in the combination have been previously cleared or approved independently as chemical sterilants. FDA also considers methods where the specific process does not appear to have been evaluated by FDA, either because the parameters of an FDA-cleared sterilizer have been altered, or because process validation data have not been evaluated and found to be adequate in previous cleared or approved submissions, to be **novel**.

Examples of Novel Sterilization Methods:

- Vaporized peracetic acid
- High intensity light or pulse light
- Microwave radiation
- Sound waves
- Ultraviolet light

V. Sterilization Information for Devices Labeled as Sterile

A. Established Sterilization Methods

Sponsors should ensure that a 510(k) submission includes all of the information outlined below.

1. For the sterilization method, the sponsor should provide the following:
   a. a description of the sterilization method;
   b. a description of the sterilization chamber if not rigid, fixed (e.g., flexible bag);
   c. for those methods described in Section IV.A.2. (**Established** Category B):
      - if the sterilizer has received 510(k) clearance,[11] the 510(k) number, and the make (i.e., manufacturer) and model of the sterilizer. Additionally, the submission should state whether or not the cycles for which the sterilizer was granted clearance have been altered;
      - if the sterilizer has not received 510(k) clearance, this should be stated;
      - if the sterilization method has been evaluated through clearance of a 510(k) or approval of a PMA or HDE for a device using that method, the submission number where the method was previously evaluated or

[11] Sterilizers intended for use in healthcare facilities require 510(k)s. Industrial sterilizers do not require 510(k)s.

the identification of a Device Master File[12] containing this information. Additionally, the submission should state whether or not the cycles that were previously evaluated in the cleared or approved submission have been altered;

d. the sterilization site;[13]
e. in the case of radiation sterilization, the radiation dose;
f. for chemical sterilants (e.g., EO, H_2O_2), the maximum levels of sterilant residuals that remain on the device, and an explanation of why those levels are acceptable for the device type and the expected duration of patient contact.

   In the case of EO sterilization, CDRH has accepted EO residuals information based on the currently recognized version of the standard, "ISO 10993-7, *Biological Evaluation of Medical Devices – Part 7: Ethylene Oxide Sterilization Residuals*."

2. For the sterilization method, the sponsor should provide a description of the method used to validate the sterilization cycle (e.g., the half-cycle method) but not the validation data itself. The submission should also identify all relevant consensus standards used and identify any aspects of the standards that were not met. In the absence of a recognized standard, a comprehensive description of the process and the complete validation protocol should be submitted and reviewed.

3. The sponsor should state the sterility assurance level (SAL) of 10^{-6} for devices labeled as sterile unless the device is intended only for contact with intact skin. FDA recommends a SAL of 10^{-3} for devices intended only for contact with intact skin. For questions related to alternative SALs, we recommend direct consultation and pre-submission meetings with FDA.[14]

4. Pyrogenicity testing is used to help protect patients from the risk of febrile reaction due to either gram-negative bacterial endotoxins or other sources of pyrogens (e.g., material-mediated pyrogens). To address the presence of bacterial endotoxins, devices that fall under the following categories should meet pyrogen limit specifications:
   - implants;
   - devices in contact directly or indirectly with the cardiovascular system, the lymphatic system, or cerebrospinal fluid, including devices that are

[12] For more information on Device Master Files, please see https://www.fda.gov/medical-devices/premarket-approval-pma/master-files

[13] The identification of the sterilization site may be provided in the sterilization section of the 510(k) submission or in Section I of Form 3514, CDRH Premarket Review Submission Cover Sheet (available at https://www.fda.gov/media/72421/download)

[14] For more information on pre-submission interactions, please see the guidance "Requests for Feedback on Medical Device Submissions: The Pre-Submission Program and Meetings with FDA Staff" (available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/requests-feedback-and-meetings-medical-device-submissions-q-submission-program)

present for similar systemic exposure; or
- devices labeled non-pyrogenic.

Note: The Agency recommends use of the expressions "non-pyrogenic" or "meets pyrogen limit specifications" instead of "pyrogen free," unless the complete removal of pyrogens can be established. In addition, for devices that should meet pyrogen limit specifications, we recommend the labeling state that the device is non-pyrogenic.

The sponsor should provide the information outlined below:

a. a description of the method used to make the determination that the device meets pyrogen limit specifications (e.g., bacterial endotoxins test (BET), also known as the *Limulus* amebocyte lysate (LAL) test);
b. a statement confirming that endotoxin testing will be conducted on every batch or if not, information regarding the sampling plan used for in-process testing and/or finished product release, as recommended in the FDA guidance, "Pyrogen and Endotoxins Testing: Questions and Answers" (https://www.fda.gov/regulatory-information/search-fda-guidance-documents/pyrogen-and-endotoxins-testing-questions-and-answers);
c. identification of the chosen testing limit; and
d. an explanation supporting the selected endotoxin limit.

We recommend the following endotoxin limits for the BET: 20 endotoxin units (EU)/Device for general medical devices (e.g., blood contacting and/or implanted) and 2.15 EU/Device for devices that contact cerebrospinal fluid. See:

- USP <161>, *Medical Devices-Bacterial Endotoxin and Pyrogen Tests*
- ANSI/AAMI ST72, *Bacterial endotoxins – Test methods, routine monitoring, and alternatives to batch testing*
- FDA's guidance "Pyrogen and Endotoxins Testing: Questions and Answers" (available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/pyrogen-and-endotoxins-testing-questions-and-answers)

Sponsors should also be aware that there are additional sources of pyrogens beyond gram-negative bacteria. Material-mediated pyrogens are chemicals that can leach from a medical device and are traditionally addressed as part of the biocompatibility assessment.

For devices that do not need to meet pyrogen limit specifications because of the nature of body contact, but are intended to be labeled as "non-pyrogenic," we recommend that both bacterial endotoxin and material mediated pyrogenicity testing be conducted.[15] For device-specific questions, please

[15] We recommend that you assess material mediated pyrogenicity using a pyrogenicity test such as the one outlined in USP <151>, *Pyrogen Test (USP Rabbit Test)*, or an equivalent validated method.

contact the relevant review branch as limits vary for specific device types.

5. The sponsor should provide a description of the packaging (sterile barrier system) and how it will maintain the device's sterility, and a description of the package test methods, but not package test data.[16]

B. Novel Sterilization Methods

In addition to the information identified in Section V.A above, the sponsor should provide the following information in a 510(k) for all novel sterilization methods:

1. a comprehensive description of the sterilization process;
2. the method used to validate the sterilization cycle (e.g., the half-cycle method);
3. the validation protocol; and
4. the sterilization validation data. The submission should also identify any applicable published scientific literature. For novel sterilization methods, FDA may also request additional information based on the specific device submitted for review.

[16] FDA recommends that package test methods include simulated distribution and associated package integrity, as well as simulated (and/or real-time) aging and associated seal strength testing, to validate package integrity and shelf life claims. Please refer to the currently FDA recognized version of the AAMI/ANSI/ISO 11607, *Packaging for terminally sterilized medical devices*, series of consensus standards.