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FDA/CDRH Webinar

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

FDA Final Guidance

Issued January 21, 2016

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

FDA Final Guidance

There is a 60-day delayed implementation period, to allow:

- **Industry to prepare prospective submissions**
- **Completion of 510(k) submissions currently under review**
- **Training of FDA review staff on new guidance & review procedures**

To be fully implemented March 21, 2016

WEBINAR OUTLINE

BACKGROUND

- **1990 — K90-1 510(k) Sterility Review Guidance**
- **2002 — Updated 510(k) Sterility Review Guidance K90-1**
- **2008 — Draft – Sterility Information in 510(k) Submissions**
- **2016 — Final – Sterility Information in 510(k) Submissions**

SCOPE

- **What is included; what is excluded**

STERILIZATION METHOD CATEGORIES

- **Definitions (terminology change)**
- **Examples**

INFORMATION TO BE INCLUDED IN SUBMISSIONS

- **Established A**
- **Established B**
- **Novel**

BACKGROUND

1990 — K90-1 — 510(k) Sterility Review Guidance

Published to bring greater consistency to the review process of 510(k) devices across divisions and product classes. All divisions to collect and analyze the same 510 (k) data for sterile devices.

2002 — Updated 510(k) Sterility Review Guidance K90-1

Issued to address several significant changes that had occurred in the regulatory environment, including enactment of the Food and Drug Administration (FDA) Modernization Act of 1997 (FDAMA).

2008 — Draft – Sterility Information in 510(k) Submissions

Proposed to address advances in sterilization technology, provide clearer definition for “Novel” sterilization methods, as well as update guidance related to pyrogenicity claims.

2016 — Final – Sterility Information in 510(k) Submissions

Revised to provide public comment resolution from the 2008 Draft, providing clarification of the scope, definition of “novel” sterilization methods, and additional guidance related to pyrogenicity; assuring 510(k) review consistency.

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.

EXCLUSIONS — *2008 DRAFT*

Outside the scope of this guidance:

1. **Processes that rely on microbial exclusion, rather than microbial inactivation.**
2. **Processes intended to sterilize medical devices that incorporate materials of animal origin.**
3. **Processes intended to be used by reprocessors of single-use devices.**
4. **Information on the cleaning, disinfecting, and sterilizing of reusable devices that are reprocessed at healthcare facilities.**

EXCLUSIONS — *2008 DRAFT*

Outside the scope of this guidance:

Processes that rely on microbial exclusion, rather than microbial inactivation.

Processes intended to sterilize medical devices that incorporate materials of animal origin.

Processes intended to be used by reprocessors of single-use devices.

Information on the cleaning, disinfecting, and sterilizing of reusable devices that are reprocessed at healthcare facilities.

EXCLUSIONS — *2016 FINAL*

Outside the scope of this guidance:

1. **Sterilizers that are themselves medical devices subject to 510(k).**
2. **Processes that rely on microbial exclusion, rather than microbial inactivation.**
3. **Processes intended to sterilize medical devices that incorporate materials of animal origin.**
4. **Processes that incorporate the use of liquid chemical sterilants.**
5. **Processes intended to be used by reprocessors of single-use devices.**
6. **Information on the cleaning, disinfecting, and sterilizing of reusable devices that are reprocessed at healthcare facilities.**

IV. Methods of Sterilization

II. METHODS OF STERILIZATION – *2008 DRAFT*

A. Definitions

1. Traditional Sterilization Methods:

2. Non-traditional Sterilization Methods:

3. Novel Non-traditional Sterilization Methods:

B. Examples of Sterilization Methods

1. Traditional

2. Non-traditional

3. Novel non-traditional

IV. METHODS OF STERILIZATION – *2016 FINAL*

A. Established Sterilization Methods:

1. **Established Category A:**

   Examples of Established Category A:

2. **Established Category B:**

   Examples of Established Category B:

B. Novel Sterilization Methods:

Examples of Novel Sterilization Methods:

IV. METHODS OF STERILIZATION - *2016*

A. Established Sterilization Methods:

1. **Established Category A: a long history of safe and effective use demonstrated by:**
    a. **ample literature,**
    b. **clearances of 510(k)s or approvals of PMAs**
    c. **satisfactory Quality Systems inspections**
    d. **FDA-recognized standards for development, validation, and routine control**

Examples of these Established Category A Sterilization Methods:

- **Dry heat**
- **Ethylene oxide (EO) in a fixed, rigid chamber**
- **Moist heat or steam**
- **Radiation (e.g., gamma, electron beam)**

IV. METHODS OF STERILIZATION - *2016*

A. Established Sterilization Methods:

2. Established Category B: methods for which

a. there are no FDA-recognized dedicated consensus standards

b. there is published information on development, validation, and routine control

c. FDA has previously evaluated sterilization development and validation data for specific sterilizers using discrete cycle parameters and determined the validation methods to be adequate

Examples of these Established Category B Sterilization Methods:

- **Hydrogen peroxide (H_2O_2)**
- **Ozone (O_3)**
- **Flexible bag systems (e.g., EO)**

IV. METHODS OF STERILIZATION - *2016*

B. Novel Sterilization Methods — newly developed methods for which there is:

a. **little or no published information,**
b. **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**
c. **no FDA-recognized dedicated consensus standards on development, validation, and routine control.**

FDA has not reviewed and determined to be adequate to effectively sterilize the device.

Examples of Novel Sterilization Methods:

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

KEY MESSAGE — Evaluation by FDA

Where the *specific process has not been evaluated by FDA* 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.

V. Sterilization Information for Devices Labeled as Sterile

ORIGINAL K90-1 — *1990*

The following information concerning the specifications related to sterility should be collected and reviewed by ODE during the review of the 510(k) for a sterile device:

- the sterilization method that will be used;
- a description of the method that will be used to validate the sterilization cycle, but not the validation data itself;
- the sterility assurance level(SAL) for the device which the firm intends to meet;
- a description of the packaging to maintain the device's sterility(this is not to include packaging integrity testing data);
- if sterilization involves ETO, the maximum levels of residues of ethylene oxide, ethylene chlorhydrin, and ethylene glycol which remain on the device;
- whether the product is "pyrogen free" and a description of the method used to make that determination;
- the radiation dose, if radiation sterilization will be used.

UPDATED K90-1 — *2002*

Regardless of the method of sterilization, ODE scientific reviewers should gather and review the following sterilization information for all 510(k)s for devices labeled as sterile:

- The sterilization method that will be used (e.g., dry heat, moist heat, EO, radiation);
- A description of the method that will be used to validate the sterilization cycle, but not the validation data itself;
- A description of the packaging to maintain the device's sterility, not including package integrity testing data;
- If sterilization involves EO, the maximum levels of residuals of EO and ethylene chlorhydrin that remain on the device (note: the ethylene glycol residual level was dropped from this updated guidance because the recognized standard, "ANSI/AAMI/ISO 10993-7:1995 Biological Evaluation of Medical Devices – Part 7: Ethylene Oxide sterilization residuals," does not include measurement of ethylene glycol residuals);
- If the product is labeled "pyrogen free," a description of the method used to make the determination, e.g., limulus amebocyte lysate (LAL);
- The SAL (e.g., 10^{-6} for all devices, except 10^{-3} for devices only contacting intact skin); and
- In the case of radiation sterilization, the radiation dose.

III. Sterilization Information for Devices Labeled as Sterile - *2008*

A. ODE and CBER scientific reviewers should evaluate traditional sterilization methods submitted in 510(k)s for the following information. ODE and CBER scientific reviewers should also document that this information was provided.

1. For the sterilant, the reviewer should document the following:

a. a description of the sterilization method;

b. in the case of radiation sterilization, the radiation dose; and

c. 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 EtO sterilization, CDRH has accepted EtO residuals information based on the recognized standard, "ANSI/AAMI/ISO 10993-7:1995 Biological Evaluation of Medical Devices – Part 7: Ethylene Oxide Sterilization Residuals."

V. Sterilization Information for Devices Labeled as Sterile - *2016*

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 Established Category B methods:**
      - **if the sterilizer has received 510(k) clearance, 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 the identification of a Device Master File 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;**
   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, "AAMI/ANSI/ISO 10993-7, Biological Evaluation of Medical Devices – Part 7: Ethylene Oxide Sterilization Residuals."**

V. Sterilization Information for Devices Labeled as Sterile - *2016*

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

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   - **d. the sterilization site;**
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   - **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, "AAMI/ANSI/ISO 10993-7, Biological Evaluation of Medical Devices – Part 7: Ethylene Oxide Sterilization Residuals."**

V. Sterilization Information for Devices Labeled as Sterile - *2016*

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d. the sterilization site;

Where the *specific process has not been evaluated by FDA*

V. Sterilization Information for Devices Labeled as Sterile - *2016*

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III. Sterilization Information for Devices Labeled as Sterile - *2008*

2. **For the sterilization method, the reviewer should document 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 aspects of the standards that were not met.**

3. **The reviewer should document the sterility assurance level (SAL) of 10^{-6} for devices labeled 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.**

V. Sterilization Information for Devices Labeled as Sterile - *2016*

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.**

UPDATED K90-1 — *2002*

Regardless of the method of sterilization, ODE scientific reviewers should gather and review the following sterilization information for all 510(k)s for devices labeled as sterile:

- The sterilization method that will be used (e.g., dry heat, moist heat, EO, radiation);
- A description of the method that will be used to validate the sterilization cycle, but not the validation data itself;
- A description of the packaging to maintain the device's sterility, not including package integrity testing data;
- If sterilization involves EO, the maximum levels of residuals of EO and ethylene chlorhydrin that remain on the device (note: the ethylene glycol residual level was dropped from this updated guidance because the recognized standard, "ANSI/AAMI/ISO 10993-7:1995 Biological Evaluation of Medical Devices – Part 7: Ethylene Oxide sterilization residuals," does not include measurement of ethylene glycol residuals);
- **If the product is labeled "pyrogen free," a description of the method used to make the determination, e.g., *limulus* amebocyte lysate (LAL);**
- The SAL (e.g., 10^{-6} for all devices, except 10^{-3} for devices only contacting intact skin); and
- In the case of radiation sterilization, the radiation dose.

III. Sterilization Information for Devices Labeled as Sterile - *2008*

4. **The reviewer should document the testing performed to demonstrate that all blood contacting devices, permanent implants, devices that contact cerebrospinal fluid, and devices labeled pyrogen free or non-pyrogenic are, in fact, non-pyrogenic. The documentation should include the following:**

   a. a description of the method used to make the determination, e.g., bacterial endotoxins test (BET), also known as the *limulus* amebocyte lysate (LAL) test;

   b. identification of the testing endpoint that was reached; and

   c. an explanation supporting the selected endpoint. We recommend the following endotoxin endpoint: 0.5 EU/ml for general medical devices (e.g., blood contacting) and 0.06 EU/ml for devices that contact cerebrospinal fluid. These endpoints assume an extraction methodology described in the guidance or standards listed below (i.e., based on a 40 ml extraction volume per device). See:

   - **FDA "Guideline on Validation of the *Limulus* Amebocyte Lysate Test as an End Product Endotoxin Test for Human and Animal Parenteral Drugs, Biological Products, and Medical Devices" (1987)**
   - **United States Pharmacopeia (USP) <85> Bacterial Endotoxins Test**
   - **ANSI/AAMI ST72:2002 Bacterial endotoxins—Test methodologies, routine monitoring, and alternatives to batch testing**

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V. Sterilization Information for Devices Labeled as Sterile - *2016*

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:**
   a. **implants;**
   b. **devices in contact directly or indirectly with the cardiovascular system, the lymphatic system, or cerebrospinal fluid, including devices that are present for similar systemic exposure; or**
   c. **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" (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM310098.pdf);**
   c. **identification of the chosen testing limit;**
   d. **an explanation supporting the selected endotoxin limit; and**
   e. **the endotoxin unit/device.**

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>, Transfusion and Infusion Assemblies and Similar Medical Devices**
- **ANSI/AAMI ST72:2011, Bacterial endotoxins – Test methods, routine monitoring, and alternatives to batch testing**
- **FDA's guidance "Pyrogen and Endotoxins Testing: Questions and Answers" (available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM310098.pdf)**

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   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" (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM310098.pdf);**
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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 38-NF 33: 2015, <161> Medical Devices — Bacterial Endotoxin and Pyrogen Tests**
- **ANSI/AAMI ST72:2011, Bacterial endotoxins – Test methods, routine monitoring, and alternatives to batch testing**
- **FDA's guidance "Pyrogen and Endotoxins Testing: Questions and Answers" 2012 (available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM310098.pdf)**

III. Sterilization Information for Devices Labeled as Sterile - *2008*

5. The reviewer should document a description of the packaging and how it will maintain the device's sterility, and a description of the package test methods, but not package test data.

V. Sterilization Information for Devices Labeled as Sterile - *2016*

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.**

V. Sterilization Information for Devices Labeled as Sterile - *2016*

A. Established Sterilization Methods

1. For the sterilization method, the sponsor should provide:
   a. a description of the sterilization method;

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.

V. Sterilization Information for Devices Labeled as Sterile - *2016*

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.

Content Changes — *2008 Draft to 2016 Final*

1. **Clarifying Nomenclature Change, from: Traditional, Non-traditional, and Novel Non-traditional, to Established A, Established B, and Novel.**

2. **Added clarification of FDA's review policy for new sterilization technologies: validation data accountability.**

3. **Pyrogenicity recommendations and information requested have been updated.**

4. **Updated guidance and expanded references.**

Questions?

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