Sterility Review of 510(k) Submissions:

Common Microbiology Issues Found in 510(k) Submissions

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Sterility Review of 510(k) Submissions

Common Sterility Issues Found in 510(k) Submissions based on:

“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”

(Also known as FDA’s “Sterile Devices Guidance”)

and

“Reprocessing Medical Devices in Health Care Settings: Validation Methods and Labeling Guidance for Industry and Food and Drug Administration Staff”

(Also known as FDA’s “Reprocessing Guidance”)

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Generalized Overview of 510(k) Submission

Sterile Devices

- Industrial Sterilization
  (e.g., Ethylene Oxide (EO), Radiation, Steam)

FDA’s Sterile Devices Guidance (2016)

Reusable Instruments

- Processed by End User
  (e.g., Cleaning and Microbicidal processing)

STERILE DEVICES GUIDANCE

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   1. Sterilization Method
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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.

* Process whereby product is sterilized within its sterile barrier system (ISO TIR11139)
IV. METHODS OF STERILIZATION

Established Category A

Established Category B

Novel Methods
IV. METHODS OF STERILIZATION

Established Sterilization Methods:

**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

Established Sterilization Methods:

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 Established Category B Sterilization Methods:

- Hydrogen peroxide (H₂O₂)
- Ozone (O₃)
- Flexible bag systems (e.g., EO)
IV. METHODS OF STERILIZATION

Novel Sterilization Methods:

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
V. Sterilization Information for Devices Labeled as Sterile
2016 Sterile Devices Guidance

Sponsors should ensure the submission includes:

1. For the sterilization method:
   a. sterilization method description; *(e.g., gamma irradiation, ethylene oxide)*
   b. chamber description, if not rigid (i.e., bag)
   c. For Established B:
      • for a cleared sterilizer, 510(k) number, make, model, and cycle altered?
      • if the sterilizer is not cleared, this should be stated;
      • if the sterilization method has been reviewed: the 510(k)/PMA/HDE number or Device Master File containing the validation evaluation. And have the cycles been altered?
   d. the sterilization site;
   e. the dose for radiation; *(e.g., 25 kGy)*
   f. for chemical sterilants, the maximum residual levels and a justification *(e.g., EO limit based on 10993-7; what does it contact, and for how long)*
2016 Sterile Devices Guidance

Sponsors should ensure the submission includes:

1. For the sterilization method:
   a. sterilization method description
   b. chamber description, if not rigid (i.e., bag)
   c. For Established B:
      • for a cleared sterilizer, 510(k) number, make, model, and cycle altered?
      • if the sterilizer is not cleared, this should be stated;
      • if the sterilization method has been reviewed: the 510(k)/PMA/HDE number or Device Master File containing the validation evaluation. And have the cycles been altered?
   d. the sterilization site;
   e. the dose for radiation;
   f. for chemical sterilants, the maximum residual levels and a justification
Sponsors should ensure the submission includes:

2. **Validation method, and relevant standards** or a comprehensive description of process/validation protocol & maybe data

3. **Sterility assurance level (SAL)** of $10^{-6}$ for devices labeled as sterile, $10^{-3}$ for devices that only contact intact skin.

4. **Pyrogenicity Claim**, if applicable:
   a description of the method, batch testing or sampling plan confirmation, the chosen testing limit and its justification, endotoxin units/device.

5. **Packaging description** and how it will maintain the device’s sterility, and a description of package test methods, but not package test data.
V. Sterilization Information for Devices Labeled Sterile

Sponsors should ensure the submission includes:

2. Validation Methods and Consensus Standards:

- EO and Steam - *Overkill* or *Half-Cycle* Method, most of the time

  - **Method 1: Dose setting using Bioburden**
  - **Method 2: Dose setting using Fraction Positive information.**
    - 2A: General Applications
    - 2B: For very low bioburden

- \( VD_{\text{max}}^{25} \) (for 25 kGy dose)
- \( VD_{\text{max}}^{SD} \) (in increments of 2.5, from 17.5 - 35 kGy)
V. Sterilization Information for Devices Labeled Sterile

Sponsors should ensure the submission includes:

2. Validation Methods and Consensus Standards:

*Examples of Current FDA-recognized versions of:*

<table>
<thead>
<tr>
<th>Method</th>
<th>Standard Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moist Heat (steam)</td>
<td>ANSI/AAMI/ISO 17665-series <em>Sterilization of health care products: Moist Heat - Requirements for development, validation, and routine control of a sterilization process for medical devices</em></td>
</tr>
<tr>
<td>Ethylene Oxide (rigid chamber)</td>
<td>ANSI/AAMI/ISO 11135 <em>Sterilization of Health-care Products: Ethylene Oxide – Requirements for the development, validation and routine control of a sterilization process for medical devices</em></td>
</tr>
<tr>
<td>Dry Heat</td>
<td>ANSI/AAMI/ISO 20857 <em>Sterilization of health care products - Dry heat - Requirements for the development, validation and routine control of a sterilization process for medical devices</em></td>
</tr>
<tr>
<td>(Almost) Everything Else</td>
<td>ANSI/AAMI/ISO 14937 <em>Sterilization of Health-care Products - General requirements for characterization of a sterilizing agent and the development, validation, and routine control of a sterilization process for medical devices</em></td>
</tr>
</tbody>
</table>

A searchable database of FDA-recognized consensus standards is available at: [https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfStandards/search.cfm](https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfStandards/search.cfm)
Sponsors should ensure the submission includes:

3. The **sterility assurance level** (SAL):

   FDA recommends a SAL of $10^{-6}$ for all devices labeled sterile.
   (Exception: a SAL of $10^{-3}$ for devices intended only for contact with intact skin.)

**Sterility Assurance Level**: is a Statement of Probability.

The SAL is a statement of the “*probability of a single viable microorganism occurring on an item after sterilization*”\(^1\)

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Sponsors should ensure the submission includes:

3. The **sterility assurance level** (SAL):

“A SAL of $10^{-6}$ means that there is less than or equal to one chance in a million that a single viable microorganism is present on a sterilized item.”

Guide to Inspections of Medical Device Manufacturers – December, 1997 – Ch. 22
http://www.fda.gov/ICECI/Inspections/InspectionGuides/ucm115021.htm

“Invasive and implantable devices should have an SAL of $10^{-6}$; that is, no more than one nonsterile unit in a million. In practice, many firms use overkill cycles which assure an even lower probability that a device will be non-sterile.”

1. ANSI/AAMI ST79:2017 “Comprehensive guide to steam sterilization and sterility assurance in health care facilities.”
V. Sterilization Information for Devices Labeled Sterile

Sponsors should ensure the submission includes:

4. A **pyrogenicity claim**: Is the test method identified?
   
   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 amoebocyte 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*;
   
   c. **identification of the chosen testing limit**
   
   d. an **explanation supporting the selected endotoxin limit**
V. Sterilization Information for Devices Labeled Sterile

Sponsors should ensure the submission includes:

4. For devices labeled non-pyrogenic, bacterial endotoxin levels are expressed in EU (Endotoxin Units):

   This could be presented as:

   • 20.0 EU/device based on the USP protocol
     (= 0.5 EU/mL based on a 40 mL extract volume)

   • 2.15 EU/device for CSF contacting devices
     (= 0.054 EU/mL (per 40 mL) for CSF contacting devices)

(The 40 mL method is per FDA’s “Guidance for Industry: Pyrogen and Endotoxins Testing: Questions and Answers” June, 2012.)
V. Sterilization Information for Devices Labeled Sterile

Sponsors should ensure the submission includes:

5. a description of the packaging and how it will maintain the device’s sterility, and the package test methods, but not package test data.\textsuperscript{13}

\textsuperscript{13} 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 current, FDA-recognized version of the AAMI/ANSI/ISO 11607-series of consensus standards.
V. Sterilization Information for Devices Labeled Sterile

Sponsors should ensure the submission includes:

5. a description of the packaging and how it will maintain the device’s sterility, and the package test methods, but not package test data.

A simple summary of the testing design is sufficient:

**PERFORMANCE**

Simulated Distribution followed by Package Integrity testing

and

**STABILITY**

Aging followed by Seal Strength testing.

Or, a statement of conformity to the AAMI/ANSI/ISO 11607 series of consensus standards would suffice.
V. Sterilization Information for Devices Labeled Sterile

Sponsors should ensure the submission includes:

5. a description of the packaging and how it will maintain the device’s sterility, and the package test methods, but not package test data.

A more comprehensive response might look like:

**PERFORMANCE**

Simulated Distribution (e.g., ASTM D4169 “Standard Practice for Performance Testing of Shipping Containers and Systems”) followed by

Package Integrity (e.g., ASTM F1929 “Standard Test Method for Detecting Seal Leaks in Porous Medical Packaging by Dye Penetration”)

and

**STABILITY**

Simulated aging (ASTM F1980-02 “Standard Guide for Accelerated Aging of Sterile Medical Device Packages”) or (and/or real-time) aging followed by

Seal strength testing (e.g., ASTM F88 “Standard Test Method for Seal Strength of Flexible Barrier Materials”)
Frequently Asked Questions

1. Are Promissory Notes acceptable (e.g., for sterilization, residuals)?
   Promissory Notes (e.g., “will be done”) are not acceptable.

2. Is declaring conformance to 10993-7 adequate for residuals?
   No. Maximum levels should be stated. Sterilants other than EO exist.

3. For Non-pyrogenic claims, do we accept LAL testing only, or do we accept rabbit test?
   We accept validated bacterial endotoxins tests. (Rabbit testing for Materials Comp.)

4. Is “Non-pyrogenic” acceptable instead of “pyrogen-free”?
   “Non-pyrogenic” is recommended. “Pyrogen-free” is hard to establish.

5. Is product adoption acceptable – into an already established, worst-case family of products with an associated validated process (e.g., a sterilization, or aeration process)?
   - Ethylene Oxide – TIR28
   - Radiation – 11137-2, Section 4.2; and TIR35
   Yes.* This is a very commonly used approach.

* On the condition of FDA recognition of a relevant standard, or SIS citation as Relevant Guidance.
Generalized Overview of a 510(k) Submission

Sterile Devices

Industrial Sterilization
(e.g., Ethylene Oxide (EO), Radiation, Steam)

FDA’s Sterile Devices Guidance (2016)

ANSI/AAMI/ISO Standards
(11135, 11137, 17665)

Reusable Instruments

Processed by End User
(e.g., Cleaning and Microbicidal processing)

FDA’s Reprocessing Guidance (2015/2017)

AAMI Guidances
(AAMI TIR12, TIR30(ST98))
III. Scope

The scope of this guidance is limited to:

1. **Reusable** medical devices *initially supplied as sterile*, requiring reprocessing for subsequent use.

2. **Reusable** medical devices *initially supplied as non-sterile*, requiring initial processing, and reprocessing for subsequent use.

3. **Reusable** medical devices to be *reused only by a single patient*, requiring reprocessing between each use.

4. **Single-use** medical devices *supplied as non-sterile*, requiring processing prior to use.
VI. FDA’s Six Criteria for Reprocessing Instructions

1. Labeling should reflect the intended use of the device.

2. All reprocessing instructions for reusable devices should advise users to thoroughly clean the device.

3. The instructions should indicate the appropriate microbicidal process ...

4. Recommendations should be technically feasible and include only devices and accessories that are legally marketed.

5. The instructions should be comprehensive – See “A”-“P.”

6. The instructions should be understandable..
Criterion 2. **All reprocessing instructions** for reusable devices **should advise users to thoroughly clean** the device.

Several factors determine effectiveness of cleaning (e.g., device design, type of soil, human factors, training), including cleaning energies:

- Thermal energy
- Chemical energy
- Mechanical energy

Each should be optimized for the cleaning challenge and material compatibility,

*... and all specifications should be provided in the labeling.*
The Importance of Specifications

“That’s not exactly what I meant when I said ‘Please Rinse’.”
Criterion 3. The instructions should indicate the **appropriate microbicidal process** for the device.

**Spaulding Classification**

**Critical Devices:**
Are introduced **directly into the bloodstream** or which contact a **normally sterile tissue or body space** during use. There is a likelihood of microbial transmission and risk of infection if the device is not sterile.

*Examples: surgical instruments*, irrigation systems for sterile instruments in sterile tissues, endoscopes used in sterile body cavities and all endoscope biopsy accessories.

*FDA recommends* thorough cleaning and sterilization *after each use.*
Criterion 4. Reprocessing instructions should be **technically feasible** and include only devices and accessories that are **legally marketed**.

**Ranges (Time and Temperature)**

FDA recommends that “ranges” **not be used** for defining sterilization cycles (e.g., 121°C - 132°C, or 3 - 4 minutes), as this implies that:

- all intermediate values have been validated
- FDA-cleared accessories exist for intermediate cycles.

**Drying Time**

Drying time specification **may be non-standard, but not a range**.

“The Agency has accepted validated drying time specifications in the labeling that exceed those found on FDA-cleared sterilizers and that require manually setting the drying time controls.”
APPENDIX C. Examples of Sterilization Cycles Used in Health Care Settings

STEAM STERILIZATION CYCLES

Table 1. Cycle Times for Gravity-Displacement Steam Sterilization Cycles

<table>
<thead>
<tr>
<th>Item</th>
<th>Exposure Time at 121°C (250°F)</th>
<th>Exposure Time at 132°C (270°F)</th>
<th>Exposure Time at 135°C (275°F)</th>
<th>Minimum Drying Times</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wrapped Instruments</td>
<td>30 minutes</td>
<td>15 minutes</td>
<td>10 minutes</td>
<td>15 - 30 minutes</td>
</tr>
<tr>
<td>Textile Packs</td>
<td>30 minutes</td>
<td>25 minutes</td>
<td>10 minutes</td>
<td>15 minutes</td>
</tr>
<tr>
<td>Wrapped Utensils</td>
<td>30 minutes</td>
<td>15 minutes</td>
<td>10 minutes</td>
<td>15 - 30 minutes</td>
</tr>
<tr>
<td>Nonporous items (e.g., instruments)</td>
<td></td>
<td></td>
<td>3 minutes</td>
<td>0 - 1 minutes</td>
</tr>
<tr>
<td>Nonporous and porous items in mixed load</td>
<td></td>
<td></td>
<td>10 minutes</td>
<td>0 - 1 minute</td>
</tr>
</tbody>
</table>

Table 2. Cycle Times for Dynamic-Air-Removal Steam Sterilization Cycles

<table>
<thead>
<tr>
<th>Item</th>
<th>Exposure Time at 132°C (270°F)</th>
<th>Exposure Time at 135°C (275°F)</th>
<th>Minimum Drying Times</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wrapped Instruments</td>
<td>4 minutes</td>
<td>3 minutes</td>
<td>20 - 30 minutes</td>
</tr>
<tr>
<td>Textile Packs</td>
<td>4 minutes</td>
<td>3 minutes</td>
<td>16 minutes</td>
</tr>
<tr>
<td>Wrapped Utensils</td>
<td>4 minutes</td>
<td>3 minutes</td>
<td>5 - 20 minutes</td>
</tr>
<tr>
<td>Nonporous items (e.g., instruments)</td>
<td>3 minutes</td>
<td>3 minutes</td>
<td>3 minutes</td>
</tr>
<tr>
<td>Nonporous and porous items in mixed load</td>
<td>4 minutes</td>
<td>3 minutes</td>
<td>N/A</td>
</tr>
</tbody>
</table>

Criterion 4. Reprocessing instructions should be **technically feasible** and include only devices and accessories that are **legally marketed**.

**EXTENDED CYCLES**

Describes any sterilization cycle that includes specifications that deviate from those found on commonly used, FDA-cleared sterilizers, and for which there are limited or no FDA-cleared sterilization accessories.

Examples include cycles with ...

- longer exposure times, or
- higher or intermediate temperatures,

than are associated with *conventional* sterilization cycles.

“Implementation of extended cycles poses serious technical challenges in health care facilities.”

Most often, devices that can be sterilized using Extended Cycles can be sterilized using conventional, Appendix C cycles (but not always).
Part-2 of Draft “Extended Cycle” Deficiency

As another alternative, if you wish to recommend any non-standard cycles because you have been unable to validate sterilization of your device using standard cycles (e.g., due to size, mass, or complexity), please provide a statement in your labeling that indicates the following:

“This [IDENTIFY THE CYCLES] sterilization cycle is not considered by the United States Food and Drug Administration (US FDA) to be a standard sterilization cycle. Users should only use sterilizers and accessories (such as sterilization wraps, sterilization pouches, chemical indicators, biological indicators, and sterilization containers) that have been cleared by the US FDA for the selected sterilization cycle specifications (time and temperature).”
Criterion 5. Reprocessing Instructions should be **Comprehensive**.

Reprocessing instructions should include the elements below.

A. Special Accessories  
B. Point-of-Use Processing  
C. Disassembly and Reassembly  
D. Method of Cleaning  
E. Cleaning Agents  
F. Rinsing  
G. Lubricating Agents  
H. Visual Inspection  
I. Method of Disinfection or Sterilization  
J. Reduction of Sterilant Residual  
K. Drying  
L. Reuse Life  
M. Additional Labeling Recommendations  
N. Patient or Lay Use  
O. Reference to Guidelines or Accessory Labeling  
P. Manufacturer’s Contact Information
Criterion 5. Reprocessing Instructions should be **Comprehensive**.

Reprocessing instructions should include:

A. **Special Accessories:**

   The instructions should describe any special cleaning and disinfection or sterilization accessories that are needed for safe reprocessing. The instructions should also identify any special tools, sizes and types of brushes, trays, test kits, specific types of sterilization wraps, containers, or protective covers. Custom brushes should be included.

   The instructions should also provide sufficient detail so that the user can purchase the correct items or identify a source for the purchase of such items.
Draft Deficiency for Omitted Wrap Specification

The sterilization instructions for [DEVICE OR COMPONENT NAME] included in your proposed labeling do not identify the sterile barrier packaging intended to maintain sterility of your devices. To support adequate sterilization and sterile storage of your device, and as recommended in Criterion 4 (Reprocessing instructions should be technically feasible and include only devices and accessories that are legally marketed) in FDA’s guidance document “Reprocessing Medical Devices in Health Care Settings: Validation Methods and Labeling” (https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM253010), please revise your device labeling to specifically recommend use of an FDA-cleared wrap, pouch, or other method of maintaining sterility for the intended sterilization cycle. This information is requested to facilitate the use of sterile packaging that will allow sterilization of your device and maintain sterility of the device prior to use.
Draft Deficiency for Omitted Mention of Trays

1. Regarding the referenced instrument trays identified in your submission, please refer to the FDA-recognized consensus standard, AAMI / ANSI ST77:2013(R)2018, “Containment devices for reusable medical device sterilization.” Accordingly:

a. Regarding the [instrument trays] mentioned in your submission:
   i. Please confirm whether or not these [instrument trays] are intended to be part of your current submission.
   ii. If so, please provide a general description of these [trays], including model numbers, materials of construction, and dimensions. Please include this information for each model, if there is more than one model for each [tray] type.
   iii. If the [trays] are not intended to be part of the submission, please identify the 510(k) number(s) for devices that have already received FDA-clearance.

b. For each [tray] that is intended to be part of your current submission:
   i. Please indicate if they are intended to be general use sterilization trays, dedicated trays, or if they are trays used by your company for multiple device systems (including this submission, which is similar to a dedicated tray).
   ii. For any tray that is intended to be a general use sterilization tray that may be used with other products, the Agency recommends that you submit a separate 510(k) premarket submission for that device.
   iii. For any tray that is included with this submission and is intended for exclusive use with the subject device, please provide all relevant instructions in the labeling, as indicated in the above mentioned standard, that are necessary to ensure proper use of the tray. Examples include:

   - The instruction “Do not stack trays during sterilization” should appear in the labeling, unless stacking has been specifically addressed in, and supported by, your validation activities.
   - Cleaning instructions that include, but are not limited to, a recommendation to “thoroughly clean” the trays. This should be followed by an inspection instruction which includes an inspection endpoint such as “visually clean,” and a subsequent recommendation to repeat specific steps if the endpoint is not met.
Criterion 5. Reprocessing Instructions should be Comprehensive.

Reprocessing instructions should include:

B. **Point-of-Use Processing**

Instructions for *prompt*, initial cleaning steps and/or measures to prevent the drying of soil prior to cleaning, to facilitate subsequent cleaning steps.

**Organic and inorganic contamination may:**

- inactivate and/or
- prevent full penetration of a disinfectant or sterilant.
Criterion 5. Reprocessing Instructions should be **Comprehensive.**

C. **Disassembly and Reassembly**

If the device has removable parts, then reprocessing instructions should include **step-by-step instructions** for disassembly and reassembly of the device to facilitate cleaning by the user. The equipment needed to perform these activities should be identified. **Diagrams, photographs, illustrations** and/or videos are recommended.

In addition, the instructions should indicate the location where the user should perform the step (e.g., at the point of use, at the designated cleaning area).

Disassembly and reassembly instructions should be **explicit, device-specific, and reflect the validation activities**. Expressions such as “disassembly, if applicable” leave the determination of “applicability” to the discretion of the user; such ambiguous language should not be used. If a device must be disassembled for cleaning, the instructions should be validated to assure that proper reassembly can be performed at the appropriate point in reprocessing. The labeling should provide the user with a validated **method to verify that reassembly has been properly performed**; this is to assure that the device is in operable condition for the next use. Instructions should also specify whether to reassemble before or after sterilization. Additionally, disassembly and reassembly instructions should include information to **inspect the device and components for wear and tear of components** that cannot be assessed in the fully assembled configuration.
Criterion 5. Reprocessing Instructions should be **Comprehensive.**

D. **Method of Cleaning**

**Manual cleaning:** labeling should specify duration of each step, temperatures, water quality, and other necessary conditions. **Repeated actuations,** flexures, and manipulations should be specified, based on validation activities.

**Automated cleaning:** labeling should specify all processing conditions, equipment settings; time, temperature, and maximum load size.

Labeling should contain comprehensive directions for each cleaning, rinsing, and drying step so users can follow the steps or program them into the washer or washer/disinfector.
Criterion 5. Reprocessing Instructions should be **Comprehensive.**

E. **Cleaning Agents**

Recommendations for use of detergents, enzymatic cleaners, and automated cleaning cycles should be consistent with directions for use of the products and devices legally marketed in the US.

**Labeling should:**

Include instructions for the preparation and use of those agents. Examples include:

- Mix one ounce of detergent per gallon of water.
- Mix according to the detergent manufacturer’s instructions.
Criterion 5. Reprocessing Instructions should be Comprehensive.

F. Rinsing

*For FINAL RINSE WATER QUALITY* for cleaning devices that are to be sterilized:

5. Remove device/components and rinse for two minutes using warm running tap water.

NOTE: Tap water *is* acceptable:

- as an intermediate cleaning rinse for devices that are to be sterilized
- as a final rinse for cleaning devices prior to high level disinfection
Criterion 5. Reprocessing Instructions should be **Comprehensive**.

F. **Rinsing**

*AAMI TIR34 “Water for the reprocessing of medical devices.”* for more information on selection of final rinse water quality.

Additionally, for some devices, the final rinse water specifications should be sufficient to remove bacterial endotoxins. (Note that tap water may contain endotoxins.)

Criterion 5. Reprocessing Instructions should be **Comprehensive.**

H. **Visual Inspection**

All cleaning instructions should include a visual inspection.

*For cleanliness*, if the device does not pass (i.e., is not visually clean), the instructions should recommend:

- that relevant cleaning **steps be repeated**, or
- **safe disposal** of the device.

*For functionality*, visual inspection instructions should provide acceptance criteria related to device performance (e.g., **unacceptable deterioration** (corrosion, pitting, cracked seals)), as well as instructions to properly dispose of devices that fail.
Criterion 5. Reprocessing Instructions should be **Comprehensive**.

I. **Method of Disinfection or Sterilization**

Steam and EO are sufficiently well-standardized among sterilizer manufacturers such that sterilization cycles may be identified by the critical cycle parameters (the accessories are, too). (See App. C).

Newer proprietary methods (e.g., H₂O₂ and O₃) have unique characteristics which vary. For these sterilization processes, the reusable device labeling should explicitly identify:

- the **manufacturer** of the sterilizer,
- the sterilizer **model**, and
- the **specific cycle identification** (name or cycle parameters).

(Accessories should be similarly labeled.)
# APPENDIX C. Examples of Sterilization Cycles Used in Health Care Settings

## STEAM STERILIZATION CYCLES

### Table 1. Cycle Times for Gravity-Displacement Steam Sterilization Cycles

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<tr>
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<tr>
<td>Wrapped Instruments</td>
<td>30 minutes</td>
<td>15 minutes</td>
<td>10 minutes</td>
<td>15 - 30 minutes</td>
</tr>
<tr>
<td>Textile Packs</td>
<td>30 minutes</td>
<td>25 minutes</td>
<td>10 minutes</td>
<td>15 minutes</td>
</tr>
<tr>
<td>Wrapped Utensils</td>
<td>30 minutes</td>
<td>15 minutes</td>
<td>10 minutes</td>
<td>15 - 30 minutes</td>
</tr>
<tr>
<td>Nonporous items (e.g., instruments)</td>
<td>3 minutes</td>
<td>3 minutes</td>
<td>0 - 1 minutes</td>
<td>0 - 1 minute</td>
</tr>
<tr>
<td>Nonporous and porous items in mixed load</td>
<td>10 minutes</td>
<td>10 minutes</td>
<td>30 minutes</td>
<td>0 - 1 minute</td>
</tr>
</tbody>
</table>

### Table 2. Cycle Times for Dynamic-Air-Removal Steam Sterilization Cycles

<table>
<thead>
<tr>
<th>Item</th>
<th>Exposure Time at 132°C (270°F)</th>
<th>Exposure Time at 135°C (275°F)</th>
<th>Minimum Drying Times</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wrapped Instruments</td>
<td>4 minutes</td>
<td>3 minutes</td>
<td>20 - 30 minutes</td>
</tr>
<tr>
<td>Textile Packs</td>
<td>4 minutes</td>
<td>3 minutes</td>
<td>5 - 20 minutes</td>
</tr>
<tr>
<td>Wrapped Utensils</td>
<td>4 minutes</td>
<td>3 minutes</td>
<td>3 minutes</td>
</tr>
<tr>
<td>Nonporous items (e.g., instruments)</td>
<td>3 minutes</td>
<td>3 minutes</td>
<td>N/A</td>
</tr>
<tr>
<td>Nonporous and porous items in mixed load</td>
<td>4 minutes</td>
<td>3 minutes</td>
<td>N/A</td>
</tr>
</tbody>
</table>

The Agency recommends, if Immediate-Use Steam Sterilization (IUSS) is included in labeling, that it be designated as ONLY for emergency situations. IUSS cycles are intended for processing devices with very short, or no drying times. (Note: IUSS is now the commonly used and recognized expression for what was previously referred to as “flash” steam sterilization.)

If you wish to include IUSS cycles in your labeling, the Agency recommends that the presentation of such cycles be:

- properly validated,
- presented in addition to validated standard cycles (rather than in lieu of),
- clearly distinguishable and designated as distinct from those standard cycles, and
- accompanied by text that clearly describes the circumstances for which they may be used (e.g., intraoperative contamination),

as the performance of IUSS presents extraordinary challenges to the monitoring and control of sterilization equipment and cycle performance which are typically accounted for during routine processing.
Draft Deficiency for Omitted Drying Time Specification

You did not provide a recommended drying time in your Sterilization section. We are concerned that moisture remaining on the product after sterilization may result in the ingress of, and contamination by, water-borne microbes. Therefore, as discussed in Criterion 5.K of FDA’s guidance document “Reprocessing Medical Devices in Health Care Settings: Validation Methods and Labeling” (available at https://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm253010.pdf), we consider drying time to be a critical consideration for the steam sterilization process (in addition to steam exposure time and temperature). Accordingly, please provide a validated drying time recommendation in your Sterilization section.
Criterion 5. Reprocessing Instructions should be **Comprehensive**.

M. **Additional Labeling Recommendations**

Devices that are *initially supplied non-sterile* to the user and require the user to sterilize the device before use should be prominently labeled

"Non-sterile"

directly on the individual device packaging (e.g., as opposed to only on the shipper carton) to ensure non-sterile product is sterilized before use.
Criterion 6. Reprocessing Instructions should be Understandable.

- Instructions should be clear, legible (i.e., reasonable font size), and provided in sequential order from the initial processing step through the terminal step.

- They should be written in simple language to the greatest extent possible, yet sufficiently detailed to explain all procedures.

- Charts, diagrams and/or device reprocessing instructions with pictures that can be posted in work stations are recommended. Web-posted pictures/diagrams of devices can also be helpful.

- Instructions may include technique diagrams or other graphics, however, all graphics should be accompanied by clarifying text.

- The instructions should be validated to ensure that users will be able to understand and to follow them.
Criterion 6. Reprocessing Instructions should be **Understandable**.

“Store in house with relative humidity less than 80%, free of corrosive gas and good ventilation.”

**24-3-2 Disinfections**

The product recommended for disinfecting is the Biocidal that can be used with the state in which we find ourselves following the instructions provided in the package.

Let's eat, Mom.
VIII. Validation of Cleaning Process

What’s the worst that could possibly happen?
VIII. Validation of Cleaning Process

What’s the worst that could possibly happen?

That, my friend, is why they invented the “Salad-Bar-Sneeze-Guard.”
VIII. Validation of Cleaning Process

A. Validation of the Cleaning Process Using Worst-Case Testing

1. Artificial Soil, Inoculation Sites, and Simulated Use
   a. Artificial Soil
   b. Inoculation Sites
   c. Simulated Use Conditions

2. Validation Protocols: Documentation of Methods Designed to Test the Cleaning Process

3. Testing: Test Types and Protocols
   a. Choice of Test Types
   b. Methods Validation
   c. Extraction Method
Confirmation that reprocessing validation has been conducted:

Deficiency description: This deficiency may be used for 510(k) submissions when the reviewer is unsure that the reprocessing instructions have been validated, but the device type is not in Appendix E of the Reprocessing Guidance and the device design and use do not warrant a complete review of reprocessing validation data.

1. CDRH’s final guidance Reprocessing Medical Devices in Health Care Settings: Validation Methods and Labeling states that “All cleaning, disinfection, and sterilization methods should be validated, and validations should be completed prior to submission of your pre-market submission. Your reprocessing instructions should reflect the validated methods.” Based on our review of your reprocessing instructions, we are unable to determine that following your instructions for use will ensure adequate reprocessing of your device for its intended use. In order to demonstrate the ability to adequately reprocess your device, please confirm that all cleaning, disinfection and sterilization methods have been validated and that your reprocessing instructions reflect the validated methods.

www.fda.gov
X. FDA Review of Reprocessing Instructions and Documentation of Reprocessing Method Validation in Submissions

A. Documentation in 510(k)s

Review of Validation of Reprocessing Instructions

FDA has identified a subset of medical devices that pose a greater likelihood of microbial transmission and represent a high risk of infection (subclinical or clinical) if they are not adequately reprocessed. See Appendix E.

The 510(k)s for these devices should include protocols and complete test reports of the validation of the cleaning instructions.
APPENDIX E. Devices for which a 510(k) Should Contain Data to Validate Reprocessing Instructions

The FDA has identified a subset of medical devices that pose a greater likelihood of microbial transmission and represent a high risk of infection (subclinical or clinical) if they are not adequately reprocessed. This identification was based on knowledge gleaned through MDRs; recalls; periodic outbreaks of microbial transmission or patient infections reported in the literature or media; reports provided by the Centers for Disease Control (CDC), the Veterans Administration (VA), and other health care settings; and manufacturer-initiated surveillance studies.

Section 3059 of the 21st Century Cures Act (Pub. L. 114-255) required FDA to publish a list of reusable medical devices for which validated reprocessing instructions and the validation data for reprocessing of the reusable device must be included in a 510(k) submission. This section also gives FDA the authority to determine that a 510(k) submission for these reusable devices are not substantially equivalent to a predicate device if the validated instructions for use and reprocessing validation data submitted as part of the 510(k) are inadequate. As required under Section 3059 of the 21st Century Cures Act, a list of these reusable devices, categorized specifically by regulation and product code (Table 1 below) or by design features for certain device types (Table 2 below), which will require validated instructions for use and validation data in their premarket notifications, was published in the Federal Register (82 FR 26807) on June 9, 2017. The tables below are consistent with this Federal Register Notice.

Reprocessing instructions for medical devices should be validated. However, because of the greater risks to the public health posed by the devices listed below, 510(k) submissions for these devices should include protocols and complete test reports of the validation of the reprocessing instructions so that FDA has the information it needs to evaluate substantial equivalence. This includes validation of the cleaning instructions as well as the disinfection or sterilization instructions. The reprocessing validation data should demonstrate that the proposed reprocessing instructions will reprocess the subject device at least as well as the reprocessing instructions for the predicate device.

Table 1 - Reusable Devices that Require Validation Data and Validated Reprocessing Instructions be Included in 510(k) Notification and upon which FDA will Determine Substantial Equivalence

<table>
<thead>
<tr>
<th>Device Type</th>
<th>Product Code</th>
<th>Device Name</th>
<th>21 CFR Section</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bronchoscopes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(flexible or</td>
<td>EOQ</td>
<td>Bronchoscope (flexible or rigid)</td>
<td>21 CFR 874.4680</td>
</tr>
<tr>
<td>rigid) and</td>
<td>PSV</td>
<td>Ultrasound bronchoscope</td>
<td>21 CFR 892.1550</td>
</tr>
<tr>
<td>accessories</td>
<td>KTI</td>
<td>Bronchoscope accessory</td>
<td>21 CFR 874.4680</td>
</tr>
<tr>
<td></td>
<td>BTG</td>
<td>Brush, biopsy, bronchoscope (non-rigid)</td>
<td>21 CFR 874.4680</td>
</tr>
<tr>
<td></td>
<td>JFE</td>
<td>Claw, foreign body, bronchoscope (non-rigid)</td>
<td>21 CFR 874.4680</td>
</tr>
<tr>
<td></td>
<td>JEL</td>
<td>Curette, biopsy, bronchoscope (rigid)</td>
<td>21 CFR 874.4680</td>
</tr>
<tr>
<td></td>
<td>BST</td>
<td>Curette, biopsy, bronchoscope (non-rigid)</td>
<td>21 CFR 874.4680</td>
</tr>
<tr>
<td></td>
<td>BWH</td>
<td>Forceps, biopsy, bronchoscope (non-rigid)</td>
<td>21 CFR 874.4680</td>
</tr>
<tr>
<td></td>
<td>JEN</td>
<td>Electrode, laryngeal-bronchial</td>
<td>21 CFR 874.4680</td>
</tr>
<tr>
<td></td>
<td>JEN</td>
<td>Electrode, laryngeal-bronchial</td>
<td>21 CFR 874.4680</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ear, Nose, and</td>
<td>EOB</td>
<td>Nasopharyngoscope (flexible or rigid)</td>
<td>21 CFR 874.4740</td>
</tr>
<tr>
<td>Throat (ENT)</td>
<td>EOG</td>
<td>Esophagoscope (flexible or rigid)</td>
<td>21 CFR 874.4740</td>
</tr>
<tr>
<td>endoscopes and</td>
<td>GCL</td>
<td>Esophagoscope, general &amp; plastic surgery</td>
<td>21 CFR 876.1500</td>
</tr>
<tr>
<td>accessories</td>
<td>FDW</td>
<td>Esophagoscope, rigid, gastro-urology</td>
<td>21 CFR 876.1500</td>
</tr>
<tr>
<td></td>
<td>EQN</td>
<td>Laryngoscope, nasopharyngoscope</td>
<td>21 CFR 874.4740</td>
</tr>
<tr>
<td></td>
<td>EYN</td>
<td>Laryngoscope, nasopharyngoscope</td>
<td>21 CFR 874.4740</td>
</tr>
<tr>
<td></td>
<td>EYY</td>
<td>Mediastinoscope, surgical, and accessories</td>
<td>21 CFR 874.4740</td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>Gastroenterology</td>
<td>FDT</td>
<td>DuodenoScope and accessories, flexible/rigid</td>
<td>21 CFR 876.1500</td>
</tr>
<tr>
<td>and Urology</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endoscopes</td>
<td>FAK</td>
<td>Panendoscope (gastrointestinal)</td>
<td>21 CFR 876.1500</td>
</tr>
<tr>
<td>that have</td>
<td>ODF</td>
<td>Mini endoscope, gastroenterology-urology</td>
<td>21 CFR 876.1500</td>
</tr>
<tr>
<td>elevator</td>
<td>FEB</td>
<td>Accessories, cleaning, for endoscopes</td>
<td>21 CFR 876.1500</td>
</tr>
<tr>
<td>channels (not</td>
<td>NZA</td>
<td>Accessories, germicide, cleaning, for endoscopes</td>
<td>21 CFR 876.1500</td>
</tr>
<tr>
<td>including</td>
<td>OUJ</td>
<td>High level disinfection instrument for</td>
<td>21 CFR 892.1570</td>
</tr>
<tr>
<td>accessories)</td>
<td></td>
<td>ultrasonic transducers, mist</td>
<td></td>
</tr>
<tr>
<td></td>
<td>NVE</td>
<td>Washer, cleaner, automated, endoscope</td>
<td>21 CFR 876.1500</td>
</tr>
<tr>
<td></td>
<td>PSW</td>
<td>High level disinfection instrument for</td>
<td>21 CFR 892.1570</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ultrasonic transducers, liquid</td>
<td></td>
</tr>
<tr>
<td></td>
<td>FDF</td>
<td>Colonscope and accessories, flexible/rigid</td>
<td>21 CFR 876.1500</td>
</tr>
<tr>
<td></td>
<td>FBD</td>
<td>Cholecystoscopy and accessories, flexible/rigid</td>
<td>21 CFR 876.1500</td>
</tr>
<tr>
<td></td>
<td>FDS</td>
<td>Gastroscopy and accessories, flexible/rigid</td>
<td>21 CFR 876.1500</td>
</tr>
<tr>
<td></td>
<td>FAE</td>
<td>Cystoscope and accessories, flexible/rigid</td>
<td>21 CFR 876.1500</td>
</tr>
<tr>
<td></td>
<td>FGB</td>
<td>Ureteroscopy and accessories, flexible/rigid</td>
<td>21 CFR 876.1500</td>
</tr>
<tr>
<td></td>
<td>ODG</td>
<td>Endoscopic ultrasonic system,</td>
<td>21 CFR 876.1500</td>
</tr>
<tr>
<td></td>
<td></td>
<td>gastroenterology-urology</td>
<td></td>
</tr>
<tr>
<td>Neurological</td>
<td>GWG</td>
<td>Endoscope, neurological</td>
<td>21 CFR 882.1480</td>
</tr>
<tr>
<td>endoscopes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(not including</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>accessories)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Water-based</td>
<td>DWC</td>
<td>Controller, Temperature, Cardiopulmonary</td>
<td>21 CFR 870.4250</td>
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<tr>
<td>heater-cooler</td>
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<td>Bypass</td>
<td></td>
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<tr>
<td>systems for use</td>
<td>DWJ</td>
<td>System, Thermal Regulating</td>
<td>21 CFR 870.5900</td>
</tr>
<tr>
<td>in operating</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>rooms</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>System, Surgical</td>
<td>NAY</td>
<td>System, Surgical, Computer Controlled Instrument</td>
<td>21 CFR 876.1500</td>
</tr>
<tr>
<td>and Computer</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Controlled</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Instrument</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arthroscopes</td>
<td>HBX</td>
<td>Arthroscopic</td>
<td>21 CFR 888.1100</td>
</tr>
<tr>
<td>and accessories</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Laporoscopic</td>
<td>GCJ</td>
<td>Laparoscope, general &amp; plastic surgery</td>
<td>21 CFR 876.1500</td>
</tr>
<tr>
<td>instruments</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>and accessories</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Electro surgical</td>
<td>OEI</td>
<td>Electro surgical, cutting &amp; coagulation &amp;</td>
<td>21 CFR 878.4400</td>
</tr>
<tr>
<td>instruments</td>
<td></td>
<td>accessories</td>
<td></td>
</tr>
</tbody>
</table>

1 For endoscopes that fall under these product codes, 510(k) submissions must include reprocessing validation data for those endoscopes which are flexible.
2 For devices that fall under these product codes, 510(k) submissions must include reprocessing validation data if the device possesses any of the design features listed in Table 2 below.

Announced in: Federal Register / Vol. 82, No. 110 / Friday, June 9, 2017 / Notices
<table>
<thead>
<tr>
<th>Table 2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Design Features Which May Pose a Challenge to Adequate Reprocessing for Arthroscopes, Laparoscopic Instruments, and Electrosurgical Instruments, and their Respective Accessories</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Feature</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lumens (especially lumens of flexible design, multiple internal lumens, lumens that are not freely accessible, bifurcated lumens, lumens with internal surfaces that are not smooth, have internal ridges or sharp angles, or are too small to permit a brush to pass through)</td>
</tr>
<tr>
<td>Hinges, depressions, joints with gaps, overlapping or butted joints that result in acute angles, or ribbed or otherwise “roughened” surfaces (e.g., jaws)</td>
</tr>
<tr>
<td>Interior device channels</td>
</tr>
<tr>
<td>Sleeves surrounding rods, blades, activators, inserters, etc.</td>
</tr>
<tr>
<td><strong>Shafts within lumens</strong></td>
</tr>
<tr>
<td>Adjacent device surfaces between which debris can be forced or caught during use</td>
</tr>
<tr>
<td>O-rings</td>
</tr>
<tr>
<td>Stopcocks/Valves</td>
</tr>
<tr>
<td>Crevices</td>
</tr>
<tr>
<td>Fittings with very close tolerances</td>
</tr>
<tr>
<td>Clamps that cannot be fully opened for cleaning</td>
</tr>
<tr>
<td>Small internal parts (e.g., springs, magnets, etc.) that may become soiled</td>
</tr>
<tr>
<td>Ridges, articulations or grooves</td>
</tr>
<tr>
<td>Rough, irregular, discontinuous surfaces that can entrap or retain soil</td>
</tr>
<tr>
<td>Capillary gaps</td>
</tr>
<tr>
<td>Luer locks</td>
</tr>
<tr>
<td>Porous materials (smooth surfaces are desirable, where possible)</td>
</tr>
<tr>
<td>Junctions between insulating sheaths and activating mechanisms (as in certain laparoscopic instruments)</td>
</tr>
<tr>
<td>Dead-ended chambers</td>
</tr>
<tr>
<td>Internal movable device components such as multiple cables</td>
</tr>
<tr>
<td>Device features that may entrap debris that can later become aerosolized (e.g., through application of power, etc.)</td>
</tr>
<tr>
<td>Devices with these or other design features that cannot be disassembled for reprocessing</td>
</tr>
</tbody>
</table>

In the future this list may be updated as additional information regarding reprocessing medical devices becomes available.
5. The instructions must be **Comprehensive**.

Example of Inadequate Instructions

**Cleaning:**

All instruments and implants that are not supplied sterile must first be cleaned using **established hospital methods** before sterilization and introduction into a sterile field. Additionally, all instruments and implants that have been previously taken into a sterile surgical field must first be cleaned using **established hospital methods** before sterilization and reintroduction into a sterile surgical field. Cleaning can include the use of neutral cleaners followed by a deionized water rinse. All products should be treated with care. Improper use or handling may lead to damage and possible improper functioning of the device.
5. The instructions must be **Comprehensive**.

Example of Inadequate Instructions

**Cleaning Instructions**

**CAUTION:** Do not use an abrasive cloth or volatile solvents to clean any portion of the .

When necessary, clean the with a soft cloth dampened with a mild cleaning solution such as green soap, green soap tincture (U.S. Pharmacopoeia), Borax, or alcohol-free hand soap. Use a fresh soft cloth dampened with sterile water to remove residue. Towel-dry or air-dry the cable.

When necessary, disinfect the using a 2% glutaraldehyde solution (such as Cidex), a bleach solution (such as 10% Sodium Hypochlorite), or a general disinfection solution approved for disinfection of external medical devices in the appropriate concentration per the product instructions for use.
<table>
<thead>
<tr>
<th>Cycle</th>
<th>Pre Vacuum Autoclave, wrapped</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Preconditioning Pulses:</strong></td>
<td>4</td>
</tr>
<tr>
<td><strong>Temperature:</strong></td>
<td>270-275°F</td>
</tr>
<tr>
<td><strong>Time:</strong></td>
<td>10 minutes</td>
</tr>
<tr>
<td>or</td>
<td></td>
</tr>
</tbody>
</table>

| Preconditioning Pulses: | 3                              |
| **Temperature:**       | 270-275°F                     |
| **Time:**              | 10 minutes                    |

Anything else?
Thank You!

U.S. FOOD & DRUG ADMINISTRATION

OHT-6
ORTHOPEDIC DEVICES