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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA-2019-N-5465]

Center for Devices and Radiological Health Ethylene Oxide Sterilization Master File Pilot Program

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration's (FDA or Agency or we) Center for Devices and Radiological Health (CDRH or Center) is announcing its Ethylene Oxide Sterilization Master File Pilot Program ("EtO Pilot Program"). The EtO Pilot Program is voluntary and intends to allow companies ("sterilization providers") that sterilize single-use medical devices using fixed chamber ethylene oxide (EtO) to submit a Master File when making certain changes between sterilization sites or when making certain changes to sterilization processes that utilize reduced EtO concentrations. Under this voluntary program, manufacturers (“PreMarket Application (PMA) holders”) of Class III devices subject to premarket approval that are affected by such changes may, upon FDA's permission, reference the Master File submitted by their sterilization provider in a postapproval report in lieu of submission of a premarket approval application (PMA) supplement. The EtO Pilot Program seeks to help ensure patient access to safe medical devices while encouraging new, innovative ways to sterilize medical devices that reduce the potential impact of EtO on the environment and on the public health while providing a regulatory approach that would address potential device shortages.

DATES: FDA is seeking participation in the voluntary EtO Pilot Program beginning [INSERT DATE OF PUBLICATION IN THE *FEDERAL REGISTER*]. See the "Participation" section for selection criteria for participation in the EtO Pilot Program and the "Procedures" section for instructions on how to submit a Master File for consideration for inclusion into the EtO Pilot Program. Up to nine eligible participants may be selected for the EtO Pilot Program.

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SUPPLEMENTARY INFORMATION:

I. Background

EtO sterilization is an important sterilization method that is widely used to keep medical devices safe. Medical devices made from certain polymers (such as plastic or resin), metals, or glass--or devices that have multiple layers of packaging or hard-to-reach crevices (such as catheters)--are often sterilized with EtO to avoid product damage during the sterilization process. It is estimated that approximately 50 percent of all sterile medical devices in the United States are sterilized using EtO (Ref. 1).

For many medical devices, sterilization with EtO may be the only method[1] currently evaluated that effectively sterilizes and does not damage the device during the sterilization process. However, there have been recent concerns about the effects of EtO exposure and environmental emissions. Earlier this year, the FDA was made aware of the closures of two device sterilization facilities due to concerns about the level of EtO emissions (Ref. 2). Since

[1] In this notice, "method" generally refers to the type of sterilization and "processes" generally refers to steps within that method to achieve a sterile device. Changes from a conventional EtO cycle to reduced/optimized EtO cycles would be considered a process change.

then, the Agency has been closely monitoring the situation and working with device manufacturers affected by the closures to minimize impact to patients who need device access. FDA continues to work with manufacturers on site changes and engage with manufacturers about potential solutions to shortage concerns. FDA has also taken several actions to advance medical device sterilization, including sponsoring two innovation challenges to identify alternatives to EtO sterilization methods (Ref. 3) and approaches to reduce EtO emissions (Ref. 4), and convening the General Hospital and Personal Use Devices Panel on November 6 to 7, 2019 (November 2019 Panel Meeting), to discuss the role of EtO sterilization in maintaining public health (84 FR 46546; see also Ref. 5).

Before most sterile medical devices are on the market, FDA reviews premarket submissions to determine if the sterility information is adequate (e.g., in accordance with internationally agreed upon voluntary consensus standards that the FDA recognizes). If a medical device manufacturer changes the method, process, or the facility identified in its original PMA submission for sterilizing its devices, the manufacturer generally needs to submit a PMA supplement so the Agency can review these changes (Ref. 6). However, considering recent events and concerns regarding EtO emissions, FDA recognizes the need to facilitate timely site changes to keep supply interruptions at a minimum and to facilitate changes to sterilization processes that utilize reduced EtO concentrations. At the November 2019 Panel Meeting, FDA received feedback from Panel members and stakeholders that the Agency could help prevent medical device shortages and advance medical device sterilization by expediting approvals of certain changes to EtO sterilization methods, processes, and facilities (Ref. 5).

For these reasons, FDA is announcing and soliciting participation in the EtO Pilot Program. Under this pilot program, sterilization providers that sterilize single-use medical

devices using fixed chamber EtO would submit a Master File when making certain changes between sterilization sites or when making certain changes to sterilization processes that utilize reduced EtO concentrations. Under this voluntary program, PMA holders of Class III devices affected by such changes may, upon FDA's permission, reference the Master File submitted by their sterilization provider in a postapproval report, in accordance with § 814.84 (21 CFR 814.84), in lieu of submission of a PMA supplement, to satisfy the requirements of § 814.39(a) and (e) (21 CFR 814.39(a) and (e)). The pilot program is intended to provide expeditious review and feedback to sterilization providers and PMA holders on Master File submissions used to support changes made to sterilization site and/or processes in a postapproval report rather than a PMA supplement. FDA intends to evaluate pilot participation and the progress of the pilot in 6 months and provide any updates to the pilot in a subsequent notice, if appropriate. This postapproval report does not remove or replace the requirement to submit periodic (annual) reports identifying changes made to the PMA under § 814.39(b). At this time, PMAs reviewed by the Center for Biologics Evaluation and Research and PMAs for combination products[2] are not eligible for this pilot.[3]

For the purposes of this document, the term "sterilization provider" is used to refer to a device manufacturer's own in-house sterilization facility or a device manufacturer's contract sterilization provider, and encompasses any subcontractor facilities utilizing the same quality system as the contract sterilization provider, as applicable. For the purposes of this document, the term "Conventional EtO cycle" is used to refer to an EtO cycle that utilizes concentrations of

[2] See 21 CFR 3.2(e).

[3] FDA is not including 510(k) devices within the scope of the pilot at this time. Manufacturers of 510(k) devices affected by such changes should evaluate the changes according to FDA's Guidance, "Deciding When to Submit a 510(k) for a Change to an Existing Device" in determining whether a new 510(k) is required (available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/deciding-when-submit-510k-change-existing-device). Generally, a new 510(k) would not be required for the types of changes subject to this pilot.

sterilant greater than 600 mg/L to sterilize medical devices, and the term "Reduced/Optimized EtO Concentration cycle" is used to refer to an EtO cycle that utilizes concentrations of sterilant significantly below 600 mg/L to sterilize medical devices.

A. Participation

Up to nine sterilization providers are eligible to participate in this voluntary EtO Pilot Program. The pilot program is limited to selected sterilization providers that follow the procedures set forth in section I.B and that also meet the following selection qualities:

1. Be a sterilization provider of a single-use device that is provided sterile;
2. Be in good compliance standing with the Agency;
3. Have an approved fixed chamber EtO sterilization process for the device in an existing PMA; and
4. Be proposing one of the following changes:
    a. A change from a Conventional EtO cycle at an existing PMA-approved sterilization site to a Conventional EtO cycle at a different site for the same sterilization provider (including EtO chamber changes within the same sterilization site);
    b. A change from a Conventional EtO cycle at an existing PMA-approved sterilization site to a Reduced/Optimized EtO Concentration cycle at the same site for the same sterilization provider; or
    c. A change from a Conventional EtO cycle at an existing PMA-approved sterilization site to a Reduced/Optimized EtO Concentration cycle at a different site for the same sterilization provider.

Sterilization processes that include cycle parameters (e.g., increased temperature, pressure, humidity) outside validated tolerances that may impact device specifications, device performance,

EtO residuals, biocompatibility or toxicology from the approved PMA device are outside the scope of the EtO Pilot Program. For site changes from a Conventional EtO cycle at an existing site to a Conventional EtO cycle at a different site (including EtO chamber changes within the same sterilization site) described in 4a above, the sterilization validation activities for the new cycle should be conducted in accordance with the validation activities in the manufacturer's approved PMA to be eligible for this pilot program. For changes from a Conventional EtO cycle to a Reduced/Optimized EtO Concentration cycle described in 4b and 4c above, the sterilization validation activities for the new cycle should conform to the FDA recognized consensus standard ISO 11135: 2014 "Sterilization of health care products--Ethylene oxide--Requirements for development, validation and routine control of a sterilization process for medical devices" to be eligible for this pilot program. Participants who do not meet these criteria will be deemed ineligible for the EtO Pilot Program.

The following are outside the scope of the EtO Pilot Program and are inappropriate for inclusion in this program:

1. Reusable devices, reprocessed single-use devices, or devices that are provided non-sterile.
2. Sterilization providers that do not have an approved fixed chamber EtO sterilization process for the device in an existing PMA.
3. Changes in contract sterilization providers or addition of a new sterilization provider using a sterilization process not approved in an existing PMA.
4. Changes to device design, specifications, or materials.
5. Packaging changes.
6. Load configuration/composition changes.
7. Sterilization processes used only for intermediate processing prior to final device assembly.

8. Devices with alternate sterility assurance levels other than 10^{-6}.
9. Devices with specialized requirements for biocompatibility or sterilant residual compatibility that differ from ISO 10993-7 "Biological evaluation of medical devices - Part 7: Ethylene oxide sterilization residuals."

B. Procedures

While the sterilization provider serves as the primary participant of the EtO Pilot Program, FDA anticipates that close collaboration between sterilization providers and PMA holders will be necessary to ensure the success of the program. Accordingly, the procedures for sterilization providers and PMA holders are set forth below.

1. Procedures for Sterilization Providers

To be considered for the voluntary EtO Pilot Program, a sterilization provider should submit the following information in a Master File for the Agency's review with a cover sheet clearly indicating "Ethylene Oxide Sterilization Master File Pilot Program" in the subject heading:

a. Name, address, and FDA Establishment Identification (FEI) number of the proposed sterilization facility.
b. List of PMA device(s) to be sterilized (identified by manufacturer, trade name, model number, and PMA number) and letter of authorization from each PMA holder for each identified device.[4]
c. Clear identification of all responsibilities of the sterilization facility and the device manufacturer.
d. Complete description of all sterilization validation information[5] used to support validation of the PMA device(s) under the proposed EtO sterilization process including:

[4] List of device(s) should reflect known devices to be sterilized at the time of submission of the Master File. Subsequent revisions to the list of device(s) should be submitted as an amendment to the Master File.
[5] Sterilization providers may wish to refer to ISO 11135:2014 for information regarding sterilization validation.

i. A risk analysis with identified risk mitigation measures to address any risks that may impact the PMA approved device with respect to its product parameters or safety and effectiveness profile.

ii. Installation Qualification, Operational Qualification, and Performance Qualification methodology.

iii. Clear, detailed product definition, along with a documented procedure for determining whether a device meets the product definition, or confirmation that the product definition has not differed from the approved PMA.

iv. All reports, protocols and process summaries presented in an easily understandable template that supports incorporation of the PMA device to be sterilized in its defined package and load configuration.

v. The process capability for the EtO sterilization process.

vi. Identification and explanation of common potential protocol deviations, along with proposed mitigation of potential deviations. The Master File should also include a strategy to address any deviations that may be subject to differences of opinion regarding safety and effectiveness between FDA and the sterilization facility and any deviations not addressed in the Master File.

vii. Identification and explanation of management structure and involvement for process and facility review.

viii. Installation and operational requalification schedule to support continuous process effectiveness.

ix. A structured program and schedule for independent audits and monitors.

e. The sterilization facility's inspectional history and history of compliance with applicable regulations (including, but not limited to, requirements under 21 CFR Parts 820 and Part 814).

For more information on Master Files, see FDA's website: https://www.fda.gov/medical-devices/premarket-approval-pma/master-files.

Upon receipt of a Master File containing the above information, FDA will determine eligibility in the pilot program by evaluating whether the criteria outlined in sections I.A and I.B.1. above have been met, and provide written feedback that either accepts the Master File into the EtO Pilot Program, or which rejects the Master File as not eligible for the pilot program. FDA intends to review the information expeditiously and make a decision within 60 days when possible. If a Master File is rejected from the program, the written feedback will identify the reasons the Master File was determined to be ineligible for the program. FDA intends to work interactively with the sponsor to address any deficiencies with the information provided in the Master File.

Sterilization providers (i.e., Master File holders) that are accepted into the pilot program should submit amendments to their Master File every 6 months with information on any process changes or new devices or PMA submissions brought into the program to maintain participation in the pilot program. If there are no modifications or changes, this should be stated in the amendment. If a sterilization provider is accepted into the pilot program or does not maintain participation, they should notify PMA holders for which they granted a right of reference to the Master File.

2. Procedures for PMA Holders

For sterilization providers to be considered for the voluntary EtO Pilot Program, PMA holders affected by a sterilization provider's participation in this program should use the following procedures. As an alternative to the submission of a PMA supplement under § 814.39(a) and (e), FDA will consider permitting PMA holders to reference the existing Master File in a postapproval

report to the Agency with a cover sheet clearly indicating "Periodic Report for Ethylene Oxide Sterilization Master File Pilot Program" in the subject heading. The postapproval report should contain the following information in lieu of the information in 21 CFR 814.84(b)(2)-(4): :

a. Name, address, and FDA FEI number of the proposed sterilization facility.
b. Master File number in which the referenced sterilization procedures are described, with signed right of reference from the Master File holder.
c. List of device(s) to be sterilized (identified by manufacturer, trade name, model number, and PMA number).

Upon receipt of a postapproval report containing the above information, FDA will advise PMA holders of whether the postapproval report is permitted as an alternate submission under § 814.39(a) and (e). Additionally, FDA will notify the PMA holder of whether the PMA, identified devices, and referenced Master File are eligible for the sterilization provider's participation in the program. If the PMA is not eligible for the sterilization provider's participation in the pilot program, FDA will notify the PMA holder of the reasons for rejection.

This Pilot Program does not otherwise remove or replace any requirements, such as, but not limited to, recordkeeping and reporting requirements, under parts 820 or 814. It is the manufacturer's responsibility to ensure compliance with applicable laws and regulations administered by FDA.

During this voluntary EtO Pilot Program, CDRH staff intends to be available to answer questions or concerns that may arise. The EtO Pilot Program participants may comment on and discuss their experiences with the Center.

II. Paperwork Reduction Act of 1995

This notice refers to previously approved collections of information found in FDA regulations. These collections of information are subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501-3521). The collections of information in part 820, regarding the Quality System regulations, have been approved under OMB control number 0910-0073. The collections of information in part 814, subparts A through E, regarding Premarket approval, have been approved under OMB control number 0910-0231.

III. References

The following references are on display in the Dockets Management Staff (see ADDRESSES), and are available for viewing by interested persons between 9 a.m. and 4 p.m., Monday through Friday; they are also available electronically at https://www.regulations.gov. FDA has verified the website addresses, as of the date this document publishes in the *Federal Register*, but websites are subject to change over time.

1. FDA, "Ethylene Oxide Sterilization for Medical Devices," available at: https://www.fda.gov/medical-devices/general-hospital-devices-and-supplies/ethylene-oxide-sterilization-medical-devices.

2. FDA, "Statement on Concerns with Medical Device Availability Due to Certain Sterilization Facility Closures," available at: https://www.fda.gov/news-events/press-announcements/statement-concerns-medical-device-availability-due-certain-sterilization-facility-closures.

3. FDA, "FDA Innovation Challenge 1: Identify New Sterilization Methods and Technologies," available at: https://www.fda.gov/medical-devices/general-hospital-devices-and-supplies/fda-innovation-challenge-1-identify-new-sterilization-methods-and-technologies.

4. FDA, "FDA Innovation Challenge 2: Reduce Ethylene Oxide Emissions," available at: https://www.fda.gov/medical-devices/general-hospital-devices-and-supplies/fda-innovation-challenge-2-reduce-ethylene-oxide-emissions

5. FDA, "November 6 to 7, 2019: General Hospital and Personal Use Devices Panel of the Medical Devices Advisory Committee Meeting Announcement," available at: https://www.fda.gov/advisory-committees/advisory-committee-calendar/november-6-7-2019-general-hospital-and-personal-use-devices-panel-medical-devices-advisory-committee.

6. FDA, "PMA Supplements and Amendments," available at: https://www.fda.gov/medical-devices/premarket-approval-pma/pma-supplements-and-amendments.

Dated: November 21, 2019.

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