A draft guidance has been issued for comment purposes only, see **Draft Guidance for Industry and FDA Staff: Submission and Review of Sterility Information in Premarket Notification (510(k)) Submissions for Devices Labeled as Sterile** issued December 12, 2008, which if issued as final, will replace the currently available guidance.

http://www.fda.gov/cdrh/ode/guidance/1615.html

Updated 510(k) Sterility Review Guidance K90-1; Guidance for Industry and FDA

Document issued on: August 30, 2002

This document supersedes 510(k) Sterility Review Guidance K90-1, dated November 16, 2001.

U.S. Department Of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health

Office of Device Evaluation

Preface

Public Comment

Comments and suggestions may be submitted at any time for Agency consideration to Dockets Management Branch, Division of Management Systems and Policy, Office of Human Resources and Management Services, Food and Drug Administration, 5630 Fishers Lane, Room 1061, (HFA-305), Rockville, MD, 20852. When submitting comments, please refer to the exact title of this guidance document. Comments may not be acted upon by the Agency until the document is next revised or updated.

For questions regarding the use or interpretation of this guidance contact Timothy A. Ulatowski at (301) 443-8879 or by email tau@cdrh.fda.gov.

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Updated 510(k) Sterility Review Guidance K90-1; Guidance for Industry and FDA

This document is intended to provide guidance. It represents the Agency's current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind the Food and Drug Administration (FDA) or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute and regulations.

I. Background

On November 16, 2001, the Office of Device Evaluation released updated review procedures regarding sterilization data submitted in premarket notification (510(k)) submissions as outlined in Blue Book Memorandum #K90-1, issued on February 12, 1990. The issuance of the November memorandum was deemed necessary given several significant changes that had occurred in the regulatory environment that had made aspects of the February 1990 memorandum obsolete. Specifically, these included:

1. Promulgation of the Quality System regulation (QS regulation, 21 CFR 820) in 1996;

2. Issuance of Blue Book Memorandum #K97-1 regarding changes to existing devices that can be made without submitting a new 510(k); and

3. Enactment of the Food and Drug Administration (FDA) Modernization Act of 1997 (FDAMA), which among many things, separated compliance with QS requirements from the substantial equivalence decision in most cases.

In 1997, the Center for Devices and Radiological Health (CDRH) decided that, given a manufacturer's obligation to comply with the QS requirements, the safety and effectiveness of a device manufacturer's sterilization process would best be ensured through compliance with the QS regulation rather than through 510(k) review. This decision was communicated to ODE staff and the medical device industry in Blue Book Memorandum #K97-1 entitled, "Deciding When to Submit a 510(k) for a Change to an Existing Device."[1] In this guidance, CDRH stated that manufacturers may modify existing devices in a number of ways, including labeling changes, technology or performance specification changes, and materials changes without submitting a new

[1] This guidance is available on CDRH's website at: http://www.fda.gov/cdrh/ode/510kmod.html

510(k) unless 'a change or the sum of the incremental changes exceeds the section 807.81(a)(3) threshold, "could significantly affect the safety or effectiveness of the device."' CDRH included changes in the sterilization method as a type of change that would not normally trip the regulatory threshold for submission of a new 510(k). As stated in the guidance, changes in sterilization processes do not require 510(k) clearance, unless the changes significantly alter the properties/specifications of a device or result in a lower sterility assurance level (SAL). In instances where a manufacturer concludes that a change in sterilization method has not significantly affected device properties/specifications or resulted in a lower SAL, no 510(k) need be submitted. Rather, the appropriate documentation must be maintained at the manufacturing site in accordance with the QS regulation requirements.

The enactment of FDAMA emphasized the separation between issues of compliance with the QS regulation and determinations of substantial equivalence (SE). In a new statutory provision, the agency was instructed not to withhold a determination of the initial classification of a device because of a failure to comply with any statutory provision unrelated to the SE decision unless "there is a substantial likelihood that the failure to comply with such regulations will potentially present a serious risk to human health." This new provision, Section 513(f)(5) of the Federal Food, Drug, and Cosmetic Act, specifically includes noncompliance with good manufacturing practices (now referred to as QS requirements) as a failure that should not ordinarily delay an SE decision. These events prompted FDA to revise its procedures for the review of sterilization information in all 510(k) submissions in 1997 and to issue the November 2001 memorandum.

In recent discussions with Center staff, it was determined that additional guidance on non-traditional methods of sterilization is needed. While the agency has experience with some types of non-traditional methods of sterilization, FDA recognizes that there may be unique or novel sterilants that have not yet been submitted in a premarket notification or that have not yet been successfully implemented by device manufacturers. Given this variety in non-traditional methods, CDRH decided that additional guidance is needed to help review staff differentiate between various types of non-traditional methods of sterilization and how applications in which they are employed should be handled.

II. Methods of Sterilization

FDA considers there to be two categories of sterilization methods used to sterilize medical devices - traditional and non-traditional. Specific methods for each category are listed below.

A. Traditional Methods of Sterilization

Traditional methods of sterilization include:

- Dry heat sterilization
- Moist heat sterilization

- Ethylene Oxide (EO) with devices placed in a fixed chamber
- Radiation (gamma and electron beam)
- Liquid chemical sterilants for sterilizing single-use devices incorporating materials of animal origin

B. Non-Traditional Methods of Sterilization

In general, methods of sterilization outside the scope of specific CDRH-recognized standards are non-traditional. A new method of sterilization remains a non-traditional method unless and until: a) the specific sterilization method is incorporated into a new or existing voluntary consensus standard formally recognized by the Agency or b) CDRH evaluates the validation data for the method of sterilization as part of a quality system evaluation and finds it satisfactory for specified types of devices.

1. As of the date of this memorandum, non-traditional methods of sterilization include:
   - EO not using a fixed chamber, e.g., EO injection into a porous polymer bag. Terms used for this process include:
     - "bag method"
     - "diffusion method"
     - "sterilization pouch"
     - "injection method"
     - "validation parts 'A' and 'B'"

     Less common indications of this type of sterilization are:
     - a long gas dwell time (>8 hours) or the absence of a specified gas dwell time
     - use of EO volume (e.g., 7.2 grains) instead of concentration (e.g., 500 – 600 mg/l)
     - mention of EO (or gas) cartridge
     - use of humidichips
     - use of "100% EO in-house"

- High intensity light
- Chlorine dioxide
- Ultraviolet light
- Combined vapor and gas plasma
- Vapor systems (e.g., peroxide or peracetic acid)
- Filtration methods
- Limited use of a liquid peracetic acid system in endoscopy and with metal instruments

2. In addition to the above non-traditional sterilization methods, ODE reviewers are occasionally presented with non-traditional methods employing a unique or novel sterilant that the agency has not previously seen in a premarket submission, for which there is no related inspectional history, or for which there is little or no published literature discussing its safety and effectiveness for its intended use. Such methods include, but are not limited to, the use of microwave radiation, pulsed light, gas plasma, and sound waves. Given that the agency has had little or no experience with these methods for achieving sterilization and is concerned about a manufacturer's ability to successfully use such methods without adversely affecting the SAL, reviewers should follow the additional procedures identified below in Section IV when reviewing a 510(k) in which a sterilization method of this type is employed.

III. Review Procedures for All Sterilization Methods

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.

IV. Additional Procedures for 510(k)s Citing Non-Traditional Sterilization Methods

As delineated in Blue Book #K97-1, a manufacturer's change in the sterilization method for an existing device will generally not require the submission of a new 510(k). Similarly, a manufacturer's use of a non-traditional sterilization method should not ordinarily effect or delay a substantial equivalence determination. In assessing the impact of a sterilization method on a device, the manufacturer should ensure that the performance characteristics have not been compromised and that the SAL remains 10^{-6} (10^{-3}, as appropriate). For 510(k)s citing a non-traditional method of sterilization, scientific reviewers should notify their Branch Chief of the pending submission and proceed as described below. Situations involving non-traditional sterilization methods should be brought to the attention of the Assistant to the Director, Office of Compliance, following the procedures below, so it can be determined whether conducting an inspection of the sterilization facility is a priority.

In order to maintain consistency in our approach to non-traditional methods of sterilization, we recommend that review scientists:

1. Identify the section in the submission related to a potential non-traditional method of sterilization;

2. Refer a copy of the section to the Branch Chief, Infection Control Devices (INCB), Division of Dental, Infection Control and General Hospital Devices (DDIGD) for consideration; and

INCB will assess the above information related to the non-traditional sterilization method and provide feedback to the referring ODE division and to OC, as needed. If INCB determines that the method is actually a traditional method, rather than a non-traditional method, then INCB will advise the referring ODE division of this determination and no referral will be made to OC.

If, however, INCB determines that the sterilization method is a non-traditional method, INCB will advise the referring ODE division and direct the information to OC for appropriate action. OC will review the information provided and consult with INCB to decide if an inspection of the sterilization facility should be considered a priority in the postmarket period. For novel, non-traditional sterilization methods for which the Agency has had limited experience (i.e., those identified in Section II, B, 2 above), INCB, along with the ODE referring division director and the ODE Deputy Director for Science and Regulatory Policy, will work with OC management to decide if an inspection may be needed in the premarket period. Throughout all of the situations described above, INCB will provide technical consultation to ODE and OC on non-traditional sterilization methods, as each situation requires.

The Least Burdensome Approach

The issues identified in this guidance document represent those that we believe need to be addressed before a device can be marketed. In developing the guidance, we carefully considered the relevant statutory criteria for Agency decision-making. We also considered the burden that may be incurred by industry's attempt to comply with the guidance and address the issues we have identified. We believe that we have considered the least burdensome approach to resolving the issues presented in the guidance document. If, however, industry believes that there is a less burdensome way to address the issues, the procedures outlined in the "A Suggested Approach to Resolving Least Burdensome Issues" document should be followed. It is available on our Center web page at: http://www.fda.gov/cdrh/modact/leastburdensome.html