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Food & Drug Administration
Dockets Management Branch
Department of Health & Human Services
CDRH/OHIP/DSMICA (HFZ-220)
1350 Piccard Drive
Rockville, MD 20850-4307

Re: Docket No. 02N-0534

Dear Sir or Madam:

We understand that the Food and Drug Administration (FDA) is developing Guidance for industry regarding validating reprocessing methods for medical devices that are cleared, or approved by FDA for single use only to implement Sections 302(b)(1)(A), 302(b)(2)(A), and 302(c)(2)(A)(xii) of the Medical Device User Fee and Modernization Act ("MDUFMA"). In furtherance of this effort, Boston Scientific Corporation ("BSC") respectfully submits these validation and routine control recommendations for FDA's consideration in developing the Guidance.

Since single-use medical devices are designed, and manufactured for one use only, extensive data should be developed for each original device model and manufacturer before attempting to validate the cleaning, disinfection, sterilization and functional performance of the reprocessed device. As you know, several European countries have banned the practice of reusing single-use medical devices due to, among other things, concerns with respect to the transfer of communicable disease. Sterilization processes validated and controlled in accordance with recognized standards should not be assumed to be effective in inactivating the causative agents of spongiform encephalopathies such as Creutzfeld-Jakob disease. The attached document includes our recommendations for the minimal validation program that must be in place to ensure reprocessed versions of single-use devices remain both safe and effective prior to being used on patients.

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VALIDATION AND ROUTINE CONTROL RECOMMENDATIONS FOR REPROCESSING MEDICAL DEVICES LABELED FOR SINGLE USE
January 21, 2003

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INTRODUCTION

This document provides recommendations for validating the reprocessing of single use devices (SUDs). The document lists the recommended general requirements for the validation and routine control of reprocessing procedures to ensure the reprocessed SUDs remain both safe and effective for multiple use. Because SUDs are not designed for reprocessing, extensive data should be developed for each original device model and manufacturer before attempting to validate the cleaning, disinfection, sterilization and performance of the reprocessed device. Accordingly, Boston Scientific urges FDA to require that, at a minimum, the following testing be included in any validation program:

(1) cleaning and sterilization characterization;
(2) microbiocidal effectiveness;
(3) product design considerations;
(4) validation of cleaning, disinfection and sterilization processes;
(5) installation, operation, and performance qualification;
(6) review and approval of validation;
(7) revalidation and equipment maintenance;
(8) safety, bioburden, and particulate testing;
(9) pyrogen validation testing;
(10) routine pyrogen testing;
(11) routine monitoring and control of processes; and
(12) product function testing.

The recommended requirements for each component are set forth below.

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VALIDATION AND ROUTINE CONTROL RECOMMENDATIONS

1. Cleaning and Sterilizing Process Characterization

The critical first step in any validation program is characterization of the cleaning and sterilization process. Characterizations of cleaning and sterilization processes must:

- Consider the longest time between devices' first use and the time cleaning is performed (including transportation), and after each use up to the maximum number of reprocessings.
- Select cleaning agents that are compatible with the device components and well characterized for organic soil removal throughout the device, including the interior surfaces. The testing should include destructive evaluation of the devices to quantify any internal residual soil.
- Select soils and perform simulated soiling to closely simulate the contamination in actual clinical use and drying types during collection and shipping until cleaning begins.
- Demonstrate the removal of the soil and cleaning residue from the device through analytical measurements.
- Demonstrate the microbiocidal effectiveness – and the factors which influence microbiocidal effectiveness – in defining sterilizing processes. To demonstrate sterilization effectiveness the worst case sterilization location in or on the device must be identified with half cycle or sublethal exposures. This may require cycle development studies with multiple inoculation and recovery tests.
- Evaluate sterility testing based on consideration of the residual soil that may remain after patient contact, storage and cleaning. Residual organic soils may significantly reduce the lethality kinetics.
- Follow industry standards for sterilization validation and demonstrate that the cycle parameters are capable of producing a sterility assurance level of at least 10E-6 under worst case sterilization chamber load conditions.
- Consider the effects of the sterilizing agent on materials, device performance, personnel safety, and environmental protection.
- Generate and document specifications for the number of sterilizing cycles allowed. Such specification should include the duration of any stated shelf life.

2. Microbiocidal Effectiveness

Studies of microbiocidal effectiveness must:

- Demonstrate the lethal action of the sterilizing agent against the type and quantity of soil and microbial contamination expected to be on the device, based on the worst case conditions.
- Identify the type of clinical organisms present, and the resistant microorganisms used, for the sterilization method selected.
- Derive an empirical mathematical relationship to define the microbial inactivation

kinetics of identified resistant microorganisms.

- Confirm that the probability of a microorganism surviving exposure to a defined treatment can be validly predicted.
- Identify the process variables that affect the lethal action of the sterilizing agent and the interactions of these process variables in relation to this lethal action.
- Assess factors that can adversely influence the effectiveness of the sterilizing agent, based upon physical and/or chemical interactions with the device and packaging, including, for example, interactions with materials and residues from manufacturing, cleaning and/or disinfection.
- Identify the processing steps employed to remove all residues.
- Identify an analytical test method (including sensitivity limits) for residue analysis, along with validation data demonstrating the absence of residues.

3. Product Design Considerations

Prior to reprocessing a SUD, the design of the predicate device must be considered. Validation testing must:

- Demonstrate that all device materials are compatible with disinfection and sterilizing agents.
- Assess factors that can adversely affect the delivery and/or distribution of the sterilizing agent, including, for example, the environment, packaging configuration(s), geometry, materials and residues from manufacturing, and cleaning and/or disinfection.
- Demonstrate that the surface and crevices within the device may be adequately cleaned.
- Demonstrate, by analysis, that the sterilant has access to all portions, including the inner surfaces and lumens of the device. Such analysis would include, for example, Scanning Electron Microscopy surface analysis of a particular device post sterilization to examine for corrosion, integrity and residual debris.
- Demonstrate that the device's specifications will not be adversely affected by reprocessing. In the event that the manufacturer responsible for performing the reprocessing (i.e., the Reprocessor) does not have access to the original manufacturer's design specifications, the Reprocessor must define and validate specifications for the device that assure its safety and effectiveness.

4. Package Design Considerations

When ethylene oxide is used to sterilize the reprocessed devices, the package system can adversely affect the delivery and/or distribution of the sterilizing agent. As a result, validation of the proposed package system must be performed, including:

- Sterility shelf life testing;
- Shipping integrity testing;
- Natural and/or accelerated aging testing; and,
- Routine testing, including testing of seal strength or packaging.

5. Validation of Cleaning, Disinfection and Sterilization Processes

All equipment used to clean and disinfect devices must be validated and controlled.

5.1 General

The purpose of validation is to demonstrate that established processes are effective and can be consistently reproduced. Validation consists of a number of identified stages: installation qualification, operational qualification, and performance qualification. Installation qualification is undertaken to demonstrate that cleaning and sterilization equipment (and any ancillary items) have been supplied and installed in accordance with specifications. Operational qualification is carried out either with unloaded equipment or using appropriate test material to demonstrate that the equipment can effect the defined cleaning or sterilization process. Performance qualification is the stage of validation that uses the product to demonstrate that the equipment consistently operates in accordance with predetermined criteria, and that the process produces a product that is clean, sterile, and meets other specified requirements.

5.2 Equipment and Installation Qualification

Qualification of equipment and installation must:

Equipment

- Establish and document the complete specification of all equipment used to deliver the sterilizing agent, including any ancillary items.
- Demonstrate that sterilization equipment complies with IEC 61010-1 and any subsequent parts of IEC 61010 that are applicable to the sterilization equipment.
- Establish and document the operating procedures for the equipment. These operating procedures shall include, but are not limited to:
  a) Step-by-step operating instructions;
  b) Fault conditions, the manner in which they are indicated and actions to be taken;
  c) Instructions for maintenance and calibration; and
  d) Details of contacts for technical support.

Installation

- Establish and document a specification for the location in which the equipment is to be installed (including any services required) and identify any special precautions and provisions (e.g., safety equipment).
- Document instructions for installation, including instructions pertinent to personnel health and safety.
- Confirm, prior to installation qualification, the calibration status of all instrumentation (including any test instruments) used for monitoring, controlling, indicating or recording.
- Demonstrate, after installation, that the equipment and any ancillary items operate as

intended.

- If applicable, establish and document conditions for the safe and appropriate storage of the sterilizing agent to ensure that its quality and composition remain within specification.

5.3 Operational Qualification

Prior to operational qualification, the calibration status of all instrumentation (including any test instruments) used for monitoring, controlling, indicating or recording shall be confirmed. Operational qualification shall demonstrate that the installed equipment is capable of delivering the specified process within defined tolerances.

5.4 Performance Qualification

Reprocessors must establish and document the manner of presenting the product for sterilization, including the orientation of product. Performance qualification must:

- Use the product for performance qualification that is packaged identically to the product that is sterilized routinely.
- Generate data to demonstrate the attainment of defined physical and/or chemical conditions, within specified tolerances, throughout the load and establish the relationship(s) between the conditions occurring at positions used routinely to monitor the processes and those conditions occurring throughout the load. This may be achieved by determining the attainment of the specified condition(s) at predetermined positions throughout the load.
- Conduct microbiological performance qualification studies in which the cleaning or sterilizing agent is delivered under worst case soil conditions designed to reduce the worst case microbial challenge to the process.
- Employ biological indicators that comply with recognized industry standards, where applicable.
- Perform sterility tests with products, not just biological indicators, subjected to total immersion sterility test conditions as specified in accordance with ISO 11737-2.
- Demonstrate that the levels of any process residues following exposure to the upper tolerances of the process parameters are below the specified limits identified in the health-based risk assessment.
- Confirm that the product meets the specified requirements for safety, quality and performance following application of the defined process at the upper (and lower when applicable) tolerances of the process parameters.

5.5 Review and Approval of Validation

Approval of the sterilization process specifications requires a documented review of the validation data to confirm the acceptability of the sterilization process. The review and approval process must:

- Document and review for acceptability information gathered or produced during installation qualification, operational qualification and performance qualification. Document the results of the acceptability review.
- Confirm that the process specification is complete, including the process parameters and their tolerances. The process specification must also include the criteria for designating an individual process used for a particular product.
- Ensure revalidation of all cleaning and sterilization equipment on an annual basis.

5.6 Revalidation and Equipment Maintenance

All cleaning and sterilization equipment must, at a minimum, be revalidated annually. The purpose of revalidation is to demonstrate that the equipment performs according to the parameters detailed in original validation studies and that there have been no inadvertent changes. The revalidation must:

- Confirm and document that maintenance procedures are performed as required by the original equipment manufacturer or according to a validated maintenance schedule.
- Confirm and document that the procedure for each planned maintenance task, and the frequency at which it is to be carried out are specified and documented.
- Confirm and document that equipment is not used to process a product unless all specified maintenance tasks have been satisfactorily completed and recorded.
- Confirm and document that records of maintenance are retained.
- Confirm and document that the maintenance scheme, procedures and records are periodically reviewed by a designated person and that the results of such reviews are documented.

6. Safety Testing

Devices must be tested to ensure compliance with ISO 10993 – Biological Evaluation of Medical Devices – Part 1: Evaluation and Testing. The testing must demonstrate that adverse leachable substances, including cleaning and disinfection chemicals, do not adversely affect the safety and biocompatibility of the device. Because chemical and material interactions are critical, it is essential to ensure that the tested devices represent all devices being reprocessed, and that the test articles are tested following complete processing. Testing must include an assessment of the level of any residues (e.g., detergents, lubricants, and germicides) remaining on the medical device after processing, including a toxicological evaluation of these residues.

7. Bioburden and Particulate Testing

Used, reprocessed devices may contain a wide range of contaminating microorganisms and residual inorganic and/or organic matter. Validation and control of the cleaning and disinfection processes used during reprocessing are therefore essential. To ensure adequate cleaning and disinfection, a program of bioburden and particulate testing must be performed.

Once the cleaning, decontamination and disinfection processes have been thoroughly

validated, baseline testing must be performed to determine the level of bioburden on the reprocessed device. A program of bioburden and particulate monitoring must be instituted once the baseline has been established and a consistent level of bioburden and particulates is achieved following the cleaning process. In addition, method validation must demonstrate the effectiveness of the test methods for recovery of bioburden and particulate.

A routine control and monitoring program must be instituted according to industry-recognized standards. For example, products resterilized with ethylene oxide (EO) must be tested monthly for bioburden and particulate levels following cleaning and disinfection. Corrective action must be performed if products do not meet the limits set in baseline studies.

8. Pyrogen Validation Testing

Pyrogen testing is material and process dependent. As a result, the product families chosen for validation testing must consist of the same materials and must be processed in the same manner. Products tested as part of routine pyrogen monitoring must be shown not to inhibit and/or enhance the pyrogen test method. Significantly, manufacturers may use different materials to manufacture similar products. Products with similar use, but material differences, must be evaluated separately.

9. Routine Pyrogen Testing

Routine control and monitoring programs must be instituted according to industry-recognized standards. Pyrogen tests must include:

- Testing and routine monitoring of feed water used to clean devices;
- Testing and routine monitoring of solutions used to clean devices;
- Testing of devices from each lot that is reprocessed. Tested devices must be representative of all devices within the lot; and
- Documentation of all test results.

10. Routine Monitoring and Control of Processes

Routine monitoring and process control are required to demonstrate that the validated and specified cleaning and sterilization process has been delivered to the product. Monitoring and process controls must include:

- Recorded measurements, supplemented as necessary by biological or chemical indicators, that demonstrate that the cleaning and sterilization process was delivered within defined tolerances.
- Recorded data demonstrating the attainment of process parameters.
- Retention of records in accordance with industry standards.
- Use of any biological indicators in routine monitoring, only in compliance with industry standards.