This guidance was written prior to the February 27, 1997 implementation of FDA's Good Guidance Practices, GGP's. It does not create or confer rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulations, or both. This guidance will be updated in the next revision to include the standard elements of GGP's.

APPLICATION OF THE DEVICE GOOD MANUFACTURING PRACTICE REGULATION TO THE MANUFACTURE OF STERILE DEVICES

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PURPOSE

The purpose of these instructions is to assist FDA field personnel in applying the device GMP regulation to inspections of manufacturers of sterile devices. File these instructions with CP7378.830 Inspection of Medical Device Manufacturers (10-24-83) for reference when conducting GMP inspections of sterile device manufacturers. The examples given concern conditions, procedures and methods that can directly affect sterility specifications. The examples are not intended to cover all possible variations in sterilization practices, and may not apply in all situations. They are general factors for use in determining whether a manufacturer's production procedures and sterilization processes are in compliance with the GMP regulation.

BACKGROUND

The GMP regulation requires that manufacturers adhere to a comprehensive quality assurance (QA) program which includes adequate environmental controls; trained personnel; maintenance and calibration of equipment; recordkeeping, packaging and labeling controls; and other measures applicable to the manufacture of medical devices. These aspects of QA are especially applicable to the manufacture of sterile medical devices. The applicability of any one aspect may vary, however, depending upon the method of sterilization and the product sterilized. For example, pyrogens are not a concern with noninvasive sterile devices such as surgical drapes, but are of concern for invasive devices such as transfusion/infusion sets, intraocular lens and devices that contact cerebral-spinal fluid.

METHODS OF STERILIZATION

Technically equivalent methods of sterilization are currently employed by the device industry. Each method offers certain advantages and disadvantages. Whichever method is used, manufacturers generally establish sterilization cycles in one of the following ways:

1. Using studies based on known bioburden (the number of microorganisms present on a device before sterilization) and the resistance of these microorganisms to the sterilant used.

2. Using traditionally accepted methods where process parameters are selected to assure that the process will inactivate high numbers of sterilant resistant microorganisms without necessarily relating the number to those microorganisms found on the product immediately before sterilization. When the process exceeds what is normally considered necessary to kill ambient microorganisms on the product, the method is referred to as "overkill".

The following is a discussion of some of the factors that must be considered when these methods are used:

BIOBURDEN STERILIZATION PROCESS

The process used is based on anticipated levels of microbial contamination on the product established by measuring the number of microorganisms on the product, and their resistance just before sterilization.

If manufacturers base their sterilization process on a determination of microbial load (bioburden), they are required, after sterilization parameters are set, to maintain the bioburden at or below this level by controlling the environment, i.e., airborne and fluidborne contaminants, equipment and personnel, or any other sources that can increase the device's microbial load. Variables that can be controlled to reduce the effect of these sources include airflow, air pressure, personnel practices and dress, material and processing equipment, general sanitation, and humidity. The bioburden on the product in its final packaging immediately before terminal sterilization is the chief concern.

Effective environmental control will include programs for: (1) monitoring the level of microbial contamination; and, (2) reducing its level by controlling the sources.

FDA does not:

(a) require that the sterilization process be established on the basis of bioburden;

(b) specify that bioburden testing is essential to all sterilization processes; and,

(c) require that biological indicators or physical/chemical dosimeters be used in all processes.

"OVERKILL" STERILIZATION PROCESSES

Where firms rely on high levels of heat, steam, radiation, gaseous sterilant, and/or prolonged periods of exposure in excess of that which is required to kill the most resistant organisms (overkill), they may allow conditions to exist which result in high microbial levels on the device before sterilization. This may result in bacterial counts too high to be destroyed by even an overkill cycle. Pyrogen-producing bacterial species may produce pyrogens and, while the bacteria will be destroyed during the cycle, the pyrogenic substances remain and make certain devices unfit for use. In addition, poor particulate control during the manufacture of intravascular devices could result in high levels of particulates which are capable of inducing thromboemboli.

Also, excessively high levels of sterilant or exposure may affect the performance, effectiveness or reliability of the finished device or its packaging.

When a manufacturer alleges use of the "overkill" approach, the investigator should document: the design of the sterilization process; procedures followed in controlling the sterilization cycle parameters; procedures for minimizing filth and particulates; and, the statistical and biological basis for any finished product sampling and testing.

VALIDATION

Process validation is a documented program which provides a high degree of assurance that a specific process will consistently produce a device meeting its predetermined specifications and quality attributes. The basic elements of this program include demonstrated equipment installation performance; demonstrated process performance; and program documentation, review, and approval.

A need for process validation is implied in the medical device GMP, 21 CFR 820. Section 820.5 requires every finished device manufacturer to ". . . prepare and implement a quality assurance program that is appropriate to the specific device manufactured. . ." Section 820.3(n) defines quality assurance as ". . .all activities necessary to verify confidence in the quality of the process used to manufacture a finished device."

Process validation is the major activity used to provide confidence that a process will consistently produce a device meeting the designed quality attributes. Section 820.100 states, "Written manufacturing specifications and processing procedures shall be established, implemented, and controlled to assure that the device conforms to its original design or any approved changes in that design." In addition, Section 820.100(b)(1) states, "Where deviations from device specifications could occur as a result of the manufacturing process itself, there shall be written procedures describing any processing controls necessary to assure conformance to specifications." This section implies the need for review of the process (revalidation) upon initiation of significant changes in product, package, equipment, or operating conditions.

Associations have published a number of validation approaches that are considered acceptable by the FDA. Verification of GMP compliance and process efficacy by FDA is based upon review of each firm's validation procedures and data.

If a firm cannot produce documentation to show that the process in use has been "validated" (i.e., determined to be capable of performing its intended function), the investigator should collect data for evaluation to determine whether the process is adequate to achieve the expected result, i.e., the process consistently produces sterile devices. Sufficient data must be obtained to provide an adequate estimate of the microbial lethality of the sterilization cycle for the devices sterilized. CP 7378.830A should be consulted for a list of the data necessary to evaluate the process. If deviations are found, the process should be treated and reported in the same way as other GMP regulation process inadequacies. Process deviations in the area of sterilization are especially significant since they have a direct and crucial impact on the safety and the conformance to specifications of a finished device.

Examples of deficiencies which may indicate that sterilization operations may not be effective include:

1. adverse FDA laboratory findings, i.e., a violative sample with a verified violative check analysis sample;

2. evidence that an abnormal percentage of lots are rejected by the manufacturers as a result of failing the USP sterility test;

3. history of frequent breakdowns, cycle failures, operating problems with sterilization equipment;

4. failure to properly maintain and calibrate instrumentation and to record such activities;

5. lack of records for the sterilization process cycle or, if relying on USP finished product testing, lack of records for device sterility testing;

6. failure to control the identification, handling and storage of finished sterile devices and failure to control lots waiting for sterility analysis (i.e., held in quarantine or stored at a controlled warehouse). Quarantined devices labeled per 801.150(e) may be moved but may not be not placed into commercial distribution;

7. lack of adequate knowledge of process controls and measurement requirements by employees who operate equipment;

8. failure of the manufacturer to follow his own procedures for sterilizing devices;

9. absence of specifications outlining the design of the sterilization process.

The district should contact FDA headquarters personnel possessing special expertise in the sterilization of devices before concluding that a manufacturer's sterilization process is inadequate.

APPLICATION OF SPECIFIC GMP REGULATION SECTIONS

The investigator should use judgment in determining if conditions, controls, and procedures are necessary to meet the intent of the GMP. In addition to coverage of the following areas, to assure complete inspectional coverage, the investigator should review CP7378.830A and complete Attachment B of that circular as thoroughly as possible. The investigator should cover all areas to which the GMPs apply, even those not directly affecting sterility.

ORGANIZATION (820.20)

Quality Assurance is defined under 820.3(n) as "all activities necessary to assure and verify confidence in the quality of the process used to

manufacture a finished device." Further, 820.5 requires that "Every finished device manufacturer shall prepare and implement a quality assurance program that is appropriate to the specific device manufactured..."

A manufacturer of sterile devices, therefore, must develop and properly implement a QA program to assure not only that the finished device conforms to configuration and performance specifications, but also that the finished device is sterile. This result is achieved by means of a sterilization process that is:

a) appropriate for the device;

b) adequately documented; and

c) properly implemented and controlled.

The manufacturer is required to develop and implement a QA program which includes a QA audit, inspection, test, and documentation program to verify that the methods, processes, personnel practices, and facilities developed and approved for the device are properly followed and maintained. Responsibilities and authorities should be specified and the QA program should be endorsed by upper management. Such an organization should also have sufficient personnel to assure that all activities required by 820.20(a) are performed.

The QA program should provide for prevention and ready detection of discrepancies between sterilization specifications and actual results and for timely corrective action. The QA program must prevent shipment of all devices for which there is evidence of nonsterility and, when applicable, pyrogenicity.

If a finished device manufacturer has sterility testing conducted by a contract laboratory, the contractor's activities are considered an extension of the finished device manufacturer's QA program. Finished device manufacturers may be in violation of 820.20(a)(4) if they fail to assure that the activities performed by the contractor are conducted in an appropriate, proper and adequate manner.

PERSONNEL (820.25)

Section 820.25(a) requires that all personnel have the necessary training to adequately perform their assigned responsibilities. For example, formal or on-the-job training is normally required for all personnel who perform the following sterilization operations:

a) arrange sterilizer loads;

b) place biological indicators or dosimeters;

c) manage pre- and post-sterility packaging and warehousing;

d) calibrate and maintain sterilization and environmental-control equipment systems; and,

e) make decisions on acceptance and rejection or need for resterilization of a lot.

Production personnel must also be trained in hygiene and clean area routine to assure that sterilization specifications are met. Instruction in these subjects should be provided and documented in accordance with 820.25. All of the specific requirements listed in 820.25(b) also apply.

BUILDINGS (820.40)

Section 820.40 requires that buildings shall be of suitable design and contain sufficient space to facilitate adequate cleaning, maintenance, and other necessary operations.

Sterile devices should be manufactured in "clean" areas designed to facilitate all operations: assembly, packaging, storage, processing, quarantine, etc. Sufficient space must be provided so that these operations can be conducted under adequate controls to avoid commingling sterile and non-sterile devices. Buildings should be constructed or modified to prevent the entrance and harboring of vermin, birds, and other pests. Adequate washrooms and toilets should be provided and segregated from production areas. Waste material should not be allowed to accumulate. Production areas should not be used for storage or as general right-of-way for personnel or transport of materials.

ENVIRONMENTAL CONTROL (820.46)

Section 820.46 requires the environment to be controlled if it can have an adverse effect on the product's fitness for use. Such controls must be monitored. Primary production areas for sterile devices normally need to be environmentally controlled to minimize risk of microbiological and particulate contamination. If, however, a device can be adequately cleaned before packaging, control of the environment may not be significant. Packaging should be conducted under clean conditions e.g., clean room, laminar flow benches, etc.

Certain sterilization methods require that the devices be "preconditioned." Preconditioning involves subjecting the device to conditions of uniform temperature and humidity for specified periods of time to enhance the sterilization effectiveness. When preconditioning is specified in the sterilization process, specifications to control the environment and the preconditioning process must be developed.

Environmental specifications, controls for maintaining these specifications, and inspections shall all be documented by the manufacturer, as required by 820.46 and 820.181.

CLEANING AND SANITATION (820.56)

Individuals are a source of both microorganism and particle contamination in the manufacture of sterile devices. Changing areas and washroom facilities should be provided and maintained in a clean and tidy condition per 820.56(a) to minimize microbiological contamination. They should be segregated from production areas.

There should be written cleaning procedures and schedules for primary manufacturing and storage areas where appropriate. These should specify cleaning materials and methods to be used, the frequency of cleaning, and the individuals responsible for performing the procedures. Failure to provide adequate written cleaning procedures and schedules is a deviation from 820.56. If personnel hygiene or facility cleanliness could compromise the effectiveness of the sterilization process, all requirements of 820.25 and 820.56 apply.

EQUIPMENT (820.60 AND 820.61)

A formal maintenance and calibration program must be developed, documented and implemented for equipment used in the sterilization process per 820.60 and 820.61. The investigator should determine the maintenance and calibration requirements applicable to the equipment involved. Items to consider are proper maintenance and calibration of the sterilizer instrumentation such as gauges, recorders and test equipment; maintenance and adjustment of package sealing equipment; and cleaning of all appropriate processing equipment.

Equipment should be designed to facilitate cleaning and to prevent foreign matter, oil, or machine lubricants from coming into contact with components, subassemblies or the finished device per 820.60.

Failure to adequately clean a sterilizer could change the effectiveness and reproducibility of the cycle. When ETO and steam sterilization are used, chambers must be periodically checked and cleaned to ensure uniformity of distribution of gas, steam, temperature, humidity, etc., which can be affected by clogged or partially obstructed drains, vents or inlets. Defective gaskets can cause pressure loss and loss of sterilant. Complete and accurate records should be present on results of calibration, maintenance checks and adjustments of sterilization equipment.

Where manufacturing residue is unavoidable, written procedures must be provided per 820.60(d) for the removal of such adverse material from the device and removal must be documented. For example, ETO residue is a manufacturing material residue which must be removed or reduced to a safe level.

ETO residue and its two major reaction products, ethylene glycol (ETG) and ethylene chlorohydrin (ETCH), may produce toxic reactions in patients. Consequently, the proposed regulation, "Ethylene Oxide, Ethylene Chlorohydrin and Ethylene Glycol Proposed Maximum Residue Limits and Maximum Levels of Exposure," was published in the June 23, 1978, Federal Register. It proposed maximum ETO residues for drugs and medical devices. (These are to be used as guidelines only.)

Special attention should be given to ensuring that a device is within safe residue limits when the "overkill" sterilization method is used and/or the product is resterilized.

It is the responsibility of the manufacturer to set ETO residue limits for the products manufactured. If a manufacturer does not follow his own specifications, the investigator is to document the reasons why the manufacturer is not following the specifications.

Manufacturers may control residue by conducting ETO residue testing or assure that residues are adequately dissipated to acceptable levels by means of controlled studies.

Aeration is the method commonly used to remove ETO residues. Aeration may be accelerated by subjecting devices to forced air ventilation. The use of ambient air requires longer aeration time. In either case, temperature, holding time and air flow rate need to be controlled. When accelerated aeration is used, these conditions can be controlled in aeration rooms or chambers. When ambient aeration is used, hold times should be established regardless of the method used.

For those manufacturers who release devices as sterile on a dosimetric basis alone, the physical/chemical dosimeters must be routinely checked against a primary standard whose accuracy has been verified and maintained.

MANUFACTURING MATERIALS (820.20(A))

In addition to assuring acceptance and rejection of component parts and materials that go into the finished device, a device manufacturer must also assure the acceptance and rejection of manufacturing materials.

Acceptance and rejection of manufacturing materials is required by 820.20(a)(2). Manufacturing materials involved in the manufacture of sterile devices include ETO, biological indicators, incubation media, deionized water, etc. These must be properly inspected and tested for identity, viability, integrity and purity as may be applicable or otherwise it must be assured that the materials meet specifications. For example, when ETO is used, the manufacturer should either receive certification that the ETO gas conforms to specifications of purity and blend or conduct tests to assure this.

If the manufacturer releases a device on the basis of biological indicators, the performance of these bioindicators must be verified through testing or by certificate of analysis.

When the sterilization cycle is based on bioburden, specifications for the control and testing of bioburden on raw materials and components should be provided where applicable. Handling and storage practices must conform to these specifications.

MANUFACTURING SPECIFICATIONS AND PROCESSES (820.100)

The Manufacturing Specifications and Processes Section of the GMP requires that "written manufacturing specifications and processing procedures shall be established, implemented, and controlled to assure that the device conforms to its original design or any approved changes in that design." The manufacturer must develop a formal procedure to ascertain the

performance and control of each sterilization parameter to ensure it will and does routinely produce the desired results. Failure to assure that a process is adequate, appropriate, consistently reproducible, and conducted properly is an indication of an inadequate QA program and irresponsble management.

Specifications must be provided for the complete sterilization operations including, when applicable, prehumidification dwell-time, loading pattern, biological indicator location, etc.

Changes to process, device and QA documentation must be conducted using a formal change system.

CRITICAL DEVICES, MANUFACTURING SPECIFICATION AND PROCESSES (820.101)

If the device is a critical device, the sterilization process and the critical operation requirements of 820.101 would normally apply. (If a non-critical device is sterilized, the sterilization process cannot be termed a critical operation because critical operations, by definition, apply only to critical devices.)

REPROCESSING (820.115 AND 820.116)

When a lot must be resterilized, 820.115, Reprocessing of devices or components applies. If the device is critical, 820.116 applies. When resterilization is conducted, the reprocessed device should be identified as resterilized, and a record maintained. Before resterilization, the manufacturer must determine the effect of reprocessing on the device, its accessories and the packaging. Depending on the method used, resterilization could result in excessive residue of gaseous sterilant and reaction products, softening or crazing of materials, discoloration of plastics, or damage to bonded or fitted joints.

LABELING (820.120)

There must be adequate controls to maintain labeling integrity and to prevent labeling mixups. Labels must be proofread before placing in inventory and checked again prior to distribution to ensure that all data entered on the labeling are correct for the device.

DEVICE PACKAGING (820.130)

Packaging is especially important. Packaging operations must be validated and the integrity of the closure must be assured before distribution. Packaging suitability should be demonstrated for the method of sterilization used and routine methods of transit and storage. Factors to consider include permeability of the packaging material and possible degradation by the sterilization process. Closures must be designed to ensure that sterility is retained up to the time of use. Packaging specifications are vital because variations in the finish, thickness, composition and other design factors can greatly alter the effectiveness of the sterilization cycle. Failure to provide adequate packaging for sterile devices is a violation of 820.130. Incoming inspection must assure that

the packaging meets the specifications of the packaging used when the sterilization cycle was qualified, i.e., configuration and material. Inspection and testing must be documented.

DISTRIBUTION (820.150)

Each manufacturer must have written procedures for warehouse control and distribution of finished sterile devices to assure that only devices approved for release are distributed (820.150). Devices under quarantine must be clearly segregated from those released from quarantine. There should be a system for assuring that the oldest sterile devices are distributed first to minimize deterioration. Except for in vitro diagnostics and intraocular lenses, there are now no requirements for expiration dating of medical devices. Expiration dates for in vitros are required by the in vitro labeling regulations, CFR 809.10.

FINISHED DEVICE INSPECTION (820.160)

Section 820.160 states that "Prior to release for distribution, each production run, lot or batch shall be checked and, where necessary, tested for conformance with device specifications... Sampling plans for checking, testing and release of a device shall be based on an acceptable statistical rationale."

Prior to release for distribution, data must be established by the manufacturer for all lots of devices purported to be sterile. The data is evidence that the approved sterilization cycle was achieved. There is no requirement that devices labeled as sterile be tested before distribution, nor, if tested, that the USP Sterility Test be used. USP Sterility Tests are referee tests and are not necessarily considered to be a release test by the USP or the FDA.

The investigator should not attempt to impose on the manufacturer any one method for determining sterility, but should collect enough data to enable the assessment of the microbiological lethality of the sterilization cycle and the methods used to challenge the cycle on a lot-by-lot basis. CP 7378.830A should be consulted for a list of the data to be collected for evaluation.

Common methods presently utilized by the industry to assess the microbiological lethality of the sterilization cycle for each lot processed include:

1. Inoculated product (either actual device or a control device which adequately represents the most difficult device to sterilize);

2. Biological indicators;

3. Physical/chemical dosimeters;

4. Finished device testing; and,

5. Evaluation of cycle parameter values.

Where testing is done to assure the microbiological lethality of the cycle, the devices must be held in quarantine or at a controlled warehouse until tests are completed and data is received to show sterility. Quarantined devices labeled per 801.150(e) may be moved but not placed into commercial distribution. Failure to meet quarantine requirements is a violation of 820.160.

CRITICAL DEVICES, FINISHED DEVICE INSPECTIONS (820.161)

When critical devices are involved, release of lots shall be authorized by signature of designated individuals per 820.161 after all acceptance records and test results have been checked to assure that release is consistent with release criteria. Nonsterility can be caused by a number of factors, including an inadequate process, inadequate or improper biological indicators, packaging damage, change in packaging, etc. All reports of nonsterile devices must be investigated to determine the cause. Failure of a firm to properly investigate cases of nonsterility, to determine the cause, and to record the investigation is a violation of 820.161 and 820.198. A record of the results of the investigation, including conclusions and follow-up, is to be documented.

DEVICE MASTER RECORD (820.181)

The device master record should include, in addition to the normal requirements of 820.181, specifications for the sterilizer and the sterilization process including values for humidity, temperature, pressure, gas concentration, dwell time, conveyor speed, etc., as applicable to the sterilization method. There should be specifications and procedures for facility cleaning, employee dress and practices, environment, packaging, labeling, quarantine, etc. There should be procedural instructions for performing the sterilization process, including proper arrangement of the sterilizer load, placement of biological indicators, identification of sterile and nonsterile product, packaging and quarantine. There should be specifications for manufacturing materials such as ETO and other gaseous materials, monitoring equipment such as dosimeters, media and biological indicators. There should be instructions for equipment calibration, checking of charts and logs, sterility assay procedures (if used), inspection and testing of package integrity, etc.

DEVICE HISTORY RECORD (820.184)

The device history record should, in addition to the history of the manufacture of the device, include the lot number and dates of sterilization and sterility testing results.

When the sterile device is a critical device, the history record must include names of the individual(s) who performed the processing and the equipment used, all inspection checks, methods and equipment used for inspection, and the date and signature of the inspecting individual.

COMPLAINT FILES (820.198)

Application of the GMP to complaint files is the same for all devices, including sterile devices.

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