Inspections, Compliance, Enforcement, and Criminal Investigations

CPG Sec. 490.200 Parametric Release – Parenteral Drug Products Terminally Sterilized by Moist Heat

Guidance for FDA Staff[1]

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This document supersedes - CPG Sec. 460.800 Parametric Release - Terminally Heat Sterilized Drug Products 10-21-87.

I. **INTRODUCTION**

This Compliance Policy Guide (CPG) provides guidance to FDA staff on how batches of sterile parenteral drug product terminally sterilized by moist heat–under certain specified conditions (i.e., parametric release)–can be released to the market without the batch sterility testing that is normally required. This CPG applies to parenteral drug products under the jurisdiction of the Center for Drug Evaluation and Research (CDER), the Center for Biologics Evaluation and Research (CBER), and the Center for Veterinary Medicine (CVM). A previous version of this CPG, numbered Section 460.800, was published in FDA's Compliance Policy Guides Manual in 1987. This CPG supersedes that document.

FDA's guidance documents, including this CPG, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. **BACKGROUND**

FDA first approved supplemental new drug applications in 1985 for certain large volume parenteral drug products that substituted parametric release for routine lot-by-lot sterility testing of the finished product. *Parametric release* is defined as a sterility assurance release program in which demonstrated control of the sterilization process enables a firm to use defined critical process control data, in lieu of the sterility test, to fulfill the intent of 21 CFR 211.167(a).

III. **POLICY**

This policy applies only to parenteral drug products that are terminally moist-heat sterilized. It does not apply to products sterilized by filtration, radiation, dry heat, or ethylene oxide. This policy does not preempt requirements of sections 505 and 512 of the Federal Food, Drug, and Cosmetic Act (the Act). For application products, a parametric release program must be included in the product's approved application (21 CFR 314.50(d)(1), 21 CFR 314.70(b), 21 CFR 514.8(b)(2)).

A firm may rely on a parametric release strategy and need not perform end-product sterility testing when the firm meets and documents assurances for both of the following conditions: First, the firm's sterility assurance program must be in a state of control.[2] Second, for application products, the firm must have submitted all appropriate regulatory filings to FDA and be operating in conformance with its approved application.[3]

A. **Sterility Assurance Program**

To establish a parametric release program, a firm should have a sterility assurance program in place that encompasses multiple, integrated CGMP systems that are in a state of control, including (1) sterilization process validation and control, (2) verification by load monitor(s), (3) a validated container/closure system, and (4) an effective Quality System.

Control of these systems would be expected for any terminally sterilized product to ensure that a properly validated sterilization cycle has been implemented and is routinely delivered to the load. In the case of a parametric release program, a sterility assurance program demonstrates both consistent process control and process understanding. For example, a formal risk assessment program to identify, control, and communicate the risks of a terminal sterilization program would significantly increase process understanding and thus confidence in the sterility assurance program.[4]

1. *Sterilization validation*

Sterilization validation should demonstrate microbial bioburden reduction consistent with existing Agency guidance to achieve a probability of non-sterile unit of 1 in 10^6 units or better.[5] Validation of any operation depends upon the use of qualified equipment designed to achieve consistent performance to expected outcomes. When bioburden is identified as a critical parameter, bioburden testing (covering total aerobic and anaerobic microorganisms along with determining their spore forming capacity) should be conducted on presterilized drug product. Bioburden testing is a routine requirement under 21 CFR 211.110(a)(6).

Robust sterilization cycles are effective at virtually eliminating the bioburden present in the load, and include substantial safety margin. If a recovered bioburden organism possesses a D-value[6] greater than the biological indicator (BI) organism used to validate the sterilization cycle and quantitative data are inadequate to calculate lethality for the higher resistance organism, then the load fails.

Cycle process parameters should be identified by the manufacturer as critical (e.g., time, temperature, pressure) or key (e.g., cooling time, heat-up time) (21 CFR 211.113(b)).

At a minimum, any firm employing parametric release must know, document, and control critical parameters to demonstrate sterilization cycle efficacy (21 CFR 211.113(b)).[7] Strict control of the critical parameters will serve as an alternate to the finished product sterility release test. Under a parametric release program, failure to meet any of the identified critical parameters would require the rejection of the load and a thorough investigation (21 CFR 211.192). Depending on the results of the investigation and the nature of the product, the rejected load could possibly be reprocessed with a second full sterilization cycle if a provision for re-sterilization is approved by the Quality Unit (21 CFR 211.115), and, for application products, if such a reprocessing step is described in the product's approved application.

In addition to the defined critical parameters which address cycle efficacy, key process parameters demonstrate a continued state of control of the sterilization operation. These parameters must be documented and defined by the firm in its manufacturing records (21 CFR 211.186 and 211.188). Investigators should not expect to see these key process parameters specified in an application. Key process parameters may include some or all of the following:

- Chamber come-up time

- Product hold times before sterilization
- Loading patterns
- Total steam flow into chamber
- Chamber integrity (leak) testing

Final disposition of the load where these key parameters have not been achieved should be supported by a suitably justified and documented rationale, as required by 21 CFR 211.192.

It is important for a firm to determine and understand the critical and key parameters for each product subject to parametric release. Critical parameters have a direct bearing on cycle efficacy, and key parameters provide important information about the control of a cycle. For example, the cycle dwell time at sterilization temperature is typically identified as a critical process parameter (i.e., release specification defined in a submission) because it has direct bearing on the cycle efficacy. The come-up time for the chamber temperature could be defined as a key process parameter because it provides important information about the control of the cycle (when compared to the come-up time for the cycle reproducibly achieved in validation studies), and it may also be indicative of the efficacy of the cycle (excessive come-up times may indicate inability to deliver sufficient heat lethality to the product to achieve sterility).

2. *Verification by load monitor*

   If a firm's sterility assurance program is in a demonstrated state of control, as defined above, an appropriate *load monitor*, considered a critical process parameter under a parametric release program, would satisfy the requirements for a laboratory test (21 CFR 211.167(a)). The load monitor, in the form of a physical temperature probe, biological indicator, or chemical indicator, can be either a direct measurement of lethality delivered to the load, or if appropriate, an indirect lethality measurement system. The load monitor(s) is placed in an appropriate position in the load based on the evaluation of development and qualification data.

   There are three typical types of load monitors that are utilized by industry in a parametric release program:

   a. A direct load monitor that uses temperature measurements in the load (actual product or surrogate containers) to directly measure temperature in order to calculate delivered lethality to the product. Temperature measurements for this purpose should be with instruments that are accurate to within +/-0.5°C or better. (Note that a 0.5°C error results in an approximate 10% error in calculated lethality near 121°C.)[6][8]
   b. A biological load monitor utilizes an actual bacterial spore population titrated to determine a minimum lethality exposure.[7][9] It is possible to use a biological load monitor as a direct load monitor (in the product) or an indirect load monitor (in the chamber).
   c. In certain instances, a chemical load monitor might also be justified. A chemical load monitor is an indirect indicator that is calibrated such that it will identify inadequate cycles and will be able to integrate over time the major factors that are indicative of process lethality.[8][10] Since a chemical load monitor does not provide a direct measurement of critical product attributes, extensive qualification and characterization of the proposed load monitor should be conducted to determine its capability and suitability for the parametric release program.

   When results of the use of a load monitor do not meet the established limits for lot release (including loss of the indicator), this should be considered a critical process parameter failure. When equipment malfunction prevents measurement of one or more critical cycle parameters, the load monitor cannot be used to evaluate cycle lethality (21 CFR 211.165(d) and (e) and 211.167).

3. *A validated container/closure system*

   The integrity of each container/closure system should be validated to demonstrate that sterility can be maintained by the container closure system (21 CFR 211.94). The ability of the container closure system to maintain sterility throughout the product's intended shelf-life or dating period should be assessed by performing either a sterility test or a container closure integrity test.[9][11]

4. *An effective Quality System*

   It is essential for a firm to establish a successful record of sterilization process control as part of its Quality System (21 CFR 211.113(b)). Production data for such an operation show that critical process parameters continue to be tightly controlled. Key parameters should also be monitored and appropriately controlled.

   As part of FDA's evaluation of the firm's Quality System, inspections should assess the firm's Quality Unit's review and approval duties, including the firm's batch disposition procedures (21 CFR 211.22). In addition, inspections should determine if the CGMP controls implemented by a firm are adequate to ensure a robust program for parametric release of a terminally moist-heat sterilized parenteral drug product, including periodic data review to monitor for process drift (21 CFR 211.180(e) and ICH Q10).[10][12]
   In addition, the inspection should verify that the firm's Quality Unit ensures that deviations or discrepancies, whether related to critical or key parameters, load monitors, or container/closure system, are appropriately investigated, with effective corrective and preventive measures implemented (21 CFR 211.192). The firm's Quality Unit should ensure that any significant change in equipment or process requires reevaluation (qualification or verification) of the equipment or process under a change control program (21 CFR 211.68 and 211.100). In many cases, this reevaluation includes use of biological indicator challenges.

B. **Documentation of Compliance with Requirements and Specifications**

For drugs requiring application approval, the application is required to contain a description of the principles of the terminal sterilization process and related summary data.[3][13] When FDA reviews this information in the application, it will assess the critical sterilization cycle parameters proposed by the applicant to ensure they are scientifically sound for achieving their goal. The application should identify the use of parametric release, in lieu of the sterility test, as the release method for a terminally moist-heat sterilized parenteral drug product.[3][14] The inspection should verify conformance with the approved application.
When an investigator encounters a parametric release product that is not required to be the subject of an approved application, the investigator should conduct the inspection using the criteria listed in this CPG and the technical information provided in relevant FDA Guidance for Industry documents.[3][15], [11][16]
If a firm chooses to use parametric release, the firm should include the following information in appropriate manufacturing records (e.g., SOPs, batch record, or release specification sheet).

1. The statement, "Meets the requirements for parametric release," should be used in lieu of a statement indicating that the product meets conventional sterility test requirements (e.g., USP) for batch release purposes.
2. A statement verifying that in the event that any critical process parameter fails to meet the established acceptance criteria, a sterility test cannot be used as an alternate test for lot release.
3. A statement committing to reject product lots that fail to meet any of the performance acceptance criteria (i.e., the established critical process parameters).

IV. REGULATORY ACTION GUIDANCE

FDA-initiated regulatory action regarding an inappropriate use of parametric release may include issuance of a warning letter, a seizure, an injunction, and/or prosecution.

The assessment of a firm's parametric release program should be a collaborative effort between the Office of Regulatory Affairs and the appropriate Center. Initial and subsequent inspections of firms employing parametric release are based on the need to demonstrate, document, and maintain control of the sterility assurance program, as described in this CPG. Any significant adverse findings in this

important area should result in an appropriate regulatory recommendation in accordance with the Regulatory Procedures Manual (RPM).[12][17] District offices should consider submitting regulatory action recommendations when any of the criteria identified in the Policy section of this CPG are not met, including the following situations:

1. A firm does not have a properly validated terminal sterilization process.
2. The process is not in a state of control, or the firm's sterility assurance program is otherwise deficient.
3. Critical process parameters have not been established or controlled.
4. A firm has not rejected lot(s) that failed to meet a critical process parameter.
5. Key process parameters are not documented in the manufacturing records.

For application products, district offices are to promptly report the following situations to the appropriate Center:

1. A firm is using a parametric release program that is not part of its approved application.
2. A firm does not adhere to an approved parametric-release protocol.

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[1] This guidance has been prepared by the Office of Manufacturing and Product Quality, Office of Compliance in the Center for Drug Evaluation and Research in cooperation with the Center for Biologics Evaluation and Research, the Center for Veterinary Medicine, and the Office of Regulatory Affairs at the Food and Drug Administration.

[2] See PDA Technical Report No. 1, Validation of Moist Heat Sterilization Processes: Cycle Design, Development, Qualification and Ongoing Control (Revised 2007); PDA Technical Report No. 30, Parametric Release of Pharmaceuticals Terminally Sterilized by Moist Heat (1999). See also: Food and Drug Administration Compliance Program Guidance Manual Program: Drug Manufacturing Inspections 7356.002.
http://www.fda.gov/downloads/ICECI/ComplianceManuals/CompliancePrograMManual/ucm125404.pdf[18]

[3] The FDA Guidance for Industry, Submission of Documentation in Applications for Parametric Release of Human and Veterinary Drug Products Terminally Sterilized by Moist Heat Processes, was finalized in February 2010, and discusses the type and suggested content of regulatory filings for parametric release. This guidance represents the Agency's current thinking on this topic. It is available at
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072180.pdf[19] or
http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/General/ucm217665.htm[20].

[4] See FDA Guidance for Industry, Sterile Drug Products Produced by Aseptic Processing—Current Good Manufacturing Practice, available at
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070342.pdf[21].

[5] See PDA Technical Report No. 1, Validation of Moist Heat Sterilization Processes: Cycle Design, Development, Qualification and Ongoing Control (Revised 2007).

[6] The product temperature profile can be converted to lethal rates which are integrated to calculate the delivered lethality based on a reference temperature (F-value). The delivered F-value is then compared with the minimum and maximum F-values obtained in qualification studies to monitor the suitability of the cycle.

[7] USP <55> Biological Indicators-Resistance Performance Tests. An FDA employee may obtain this reference through the FDA Library.

[8] See ISO 15882:2008E for chemical monitors. An FDA employee may obtain this reference through the FDA Library

[9] See FDA Guidance for Industry, Container and Closure System Integrity Testing in Lieu of Sterility Testing as a Component of the Stability Protocol for Sterile Products, available at
http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM146076.pdf[22].

[10] See FDA Guidance for Industry, Q10 Pharmaceutical Quality System
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073517.pdf[23] and Guidance for Industry Quality Systems Approach to Pharmaceutical CGMP Regulations
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070337.pdf[24].

[11] See also FDA Guidance for Industry, Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products, available at
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072171.pdf[25].

[12] See RPM at
http://www.fda.gov/ICECI/ComplianceManuals/RegulatoryProceduresManual/default.htm[26].

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