Guidance for Industry

Submission of Documentation in Applications for Parametric Release of Human and Veterinary Drug Products Terminally Sterilized by Moist Heat Processes

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Veterinary Medicine (CVM)
Center for Biologics Evaluation and Research (CBER)

February 2010
CMC

Guidance for Industry

Submission of Documentation in Applications for Parametric Release of Human and Veterinary Drug Products Terminally Sterilized by Moist Heat Processes

Additional copies are available from:

Office of Communications
Division of Drug Information
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue
Bldg. 51, rm. 2201
Silver Spring, MD 20993-0002
(Tel) 301-796-3400
http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm
and/or
Communications Staff, HFV-12
Center for Veterinary Medicine
Food and Drug Administration
7519 Standish Place, Rockville, MD 20855
(Tel) 240-276-9300
http://www.fda.gov/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/default.htm
and/or
Office of Communication, Outreach, and
Development, HFM-40
Center for Biologics Evaluation and Research
Food and Drug Administration
1401 Rockville Pike, Suite 200N, Rockville, MD 20852-1448
(Tel) 800-835-4709 or 301-827-1800
ocod@fda.hhs.gov
http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/default.htm

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Veterinary Medicine (CVM)
Center for Biologics Evaluation and Research (CBER)

February 2010
CMC

Contains Nonbinding Recommendations

TABLE OF CONTENTS

Guidance for Industry[1]
Submission of Documentation in Applications for Parametric Release of Human and Veterinary Drug Products Terminally Sterilized by Moist Heat Processes

This guidance represents the Food and Drug Administration's (FDA'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 FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

This guidance provides recommendations to applicants on information to include in support of parametric release for sterile products[2] terminally sterilized by moist heat when submitting a new drug application (NDA), abbreviated new drug application (ANDA), new animal drug application (NADA), abbreviated new animal drug application (ANADA), biologics license application (BLA), or supplement or other postmarketing report.

Currently, FDA requires that sterile products meet certain sterility requirements before release to the market.[3, 4] In many cases, the requirements for batch release are fulfilled by conducting a sterility test on finished units drawn from the batch. *Parametric release* is defined as a sterility assurance release program where demonstrated control of the sterilization process enables a firm to use defined critical process controls, in lieu of the sterility test, to fulfill the intent of 21 CFR 211.165(a), and 211.167(a).[5] Under this strategy, market release of terminally sterilized products can be based upon meeting the defined sterilization parameters and not on performing an approved sterility test. Meeting the requirements of the parametric release process can provide greater assurance that a batch meets the sterility requirement than can be achieved with a sterility test of finished units drawn from the batch.

[1] This guidance has been prepared by the Office of Pharmaceutical Science in the Center for Drug Evaluation and Research (CDER) in cooperation with CDER's Office of Compliance, the Center for Veterinary Medicine (CVM), and the Center for Biologics Evaluation and Research (CBER) at the Food and Drug Administration.

[2] The term *product* includes final products that are regulated by CDER, CVM, and CBER.

[3] See 21 CFR 314.50(d)(1)(ii)(a) or 21 CFR 514.1(b)(5)(vii)(b).

[4] See 21 CFR 211.167(a) for drug products or 21 CFR 610.12 for biologic products. In addition, refer to United States Pharmacopeia (USP) General Chapters: <1> (Injections), <71> (Sterility), and <1041> (Biologics). Short-lived radiopharmaceuticals, including positron emission tomography (PET) drugs, are subject to sterility testing; however, they may be released prior to completion of this test (21 CFR 211.165(a)).

[5] For information on how current good manufacturing practices will be applied for products subject to parametric release that are within the scope of this guidance, see the FDA Compliance Policy Guide (CPG) 460.800.

This guidance does not provide information on procedures, studies, or data concerning efficacy and qualification/validation of moist heat sterilization processes. This guidance also does not provide information on sterility assurance validation programs. However, you may find information relating to such topics in the Agency's guidance for industry on *Submission of Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products*.[6, 7] Current Good Manufacturing Practices (CGMP) requirements for process validation are found at 21 CFR 211.100 and, for sterile products in particular, at 21 CFR 211.113(b). Adherence to CGMPs is required for all marketed products.

The principles in the guidance may also be applicable to products sterilized by other terminal sterilization processes, such as radiation sterilization, which may be suitable for parametric release. For these types of applications, we recommend the applicant discuss with the review division whether applying the guidance would be appropriate.

FDA's guidance documents, including this guidance, 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

Sterility testing by cultivation of finished units drawn from the batch is limited in its ability to detect contamination because of the following: (1) the small number of samples required for testing, which restricts the ability to capture those microorganisms dispersed in a large volume, and (2) the limited ability of the prescribed culture media to stimulate growth of all potential microorganisms. Typically, these tests will detect only major errors in the manufacturing process that result in contamination of a large number of product units. However, data derived from in-process controls of a validated terminal sterilization process can provide more accurate information regarding product sterility because the probability of product bioburden surviving the sterilization process in any single unit of a product can be calculated to be less than one in a million.

Parametric release allows manufacturers to replace sterility testing of samples drawn from the finished product as a release criterion with acceptance criteria for the control of identified process parameters. These parameters, called *critical parameters*, are critical to a successful sterilization process and are based on an in-depth knowledge of the process, the product, the

[6] This guidance outlines the submission documentation for microbiological product quality of sterile products.

[7] CDER guidance documents can be found on the Internet at *http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm*. We update guidances periodically. To make sure you have the most recent version of a guidance, check the CDER guidance Web site. CVM guidance documents can be found at *http://www.fda.gov/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/default.htm*, and CBER guidance documents can be found at *http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/default.htm*.

effects of the sterilization process on the product itself, and any microorganisms that become associated with the product during the manufacturing process. Parametric release of the batch is then based on documented evidence of the control of critical parameters, removing the need to test samples drawn from the finished product.

A *sterilization load monitor*,[8] either in the form of a physical, chemical (ANSI 2008), or biological indicator, is included with each load to satisfy the requirement for a laboratory test.[9] In addition, the sterilization load monitor is always considered a critical process parameter. A successful load monitor result, the meeting of the acceptance criteria of the critical parameters, and having a well validated sterility assurance program demonstrate that there is a state of control of the manufacturing process for the product. The load monitor(s) should be placed in appropriate positions to indicate that the load was exposed to a sterilization process which was measured and recorded for conformance with defined criteria for parametric release. This position(s) is determined based on the evaluation of development and qualification data. The location and number of monitors should be described and justified in the application. Alternative procedures for demonstrating that a load or part of a load was exposed to a sterilization process should be discussed with the review division(s) prior to submitting a plan for parametric release.

FDA conducts scientific evaluation of the parametric release program as part of a cooperative effort among our review staff, compliance staff, and field investigators.

FDA has accepted the practice of parametric release for drug products terminally sterilized by moist heat since 1985. Parametric release, described in the International Conference on Harmonisation (ICH) Q6A (ICH 2000),[10] is endorsed by regulatory and/or pharmaceutical manufacturing groups in the US (PDA 1999, USP 2009), EU (PIC/S 2007, EMEA 2001), and Japan (Sasaki 2002).

III. CONTENT OF SUBMISSIONS FOR PARAMETRIC RELEASE

Section IV describes what submissions are required to obtain approval for parametric release.[11] The approval of parametric release practices is based on an assessment of the applicant's proposed critical process parameters and how they are controlled. Demonstrated reliability of the production terminal sterilization cycle, microbiological control, and monitoring and control of production cycle parameters within established validated limits are part of this assessment. The terminal sterilization process for the product proposed for parametric release should be validated according to the Agency's guidance for industry on *Submission of Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products.*[12]

[8] See section III. C., bullet 5.
[9] See 21 CFR 211.167(a).
[10] See footnote 7.
[11] See 21 CFR 314.50(d)(1)(ii)(a) and 21 CFR 314.70(b)(2)(iii) for human drug products; 21 CFR 514.1(b)(5)(vii)(b) and 21 CFR 514.8(b)(2)(ii)(C) for veterinary drug products; or 21 CFR 601.2(a) for biologic products.
[12] See footnotes 6 and 7.

FDA approval of the parametric release program will be based on how well the firm has addressed the risks to product sterility. A risk assessment statement consistent with the principles of ICH Q9 (ICH 2006) should be provided that describes the following:

- Current strategies for control of the terminal sterilization program;
- Risk that these strategies might fail to ensure sterility; and
- How prior manufacturing experience and knowledge were incorporated into the risk assessment.[13]

A. Control Strategy for the Terminal Sterilization Program

A control strategy is used to ensure that the acceptance criteria of the parametric release process and terminal sterilization cycle are met in order to ensure product sterility.

The control strategy should include the following:

- The rationale for the methods implemented to monitor and control the terminal sterilization process used for the product release (the critical process parameters);
- The rationale for the selection of critical process parameter(s);
- A description of the acceptance criteria for parametric release;
- A description of the drug product and container closure system (including secondary packaging, as applicable) that will be part of the parametric release program;
- A description of the proposed production loading patterns and verification that they are within the validated limits for the terminal sterilization cycle, or a statement that they have not changed since last approved and validated (as applicable); and
- A description of the microbiological monitoring plan for the product and components prior to terminal sterilization or a statement that the plan has not changed since last validated. Spore detection and heat resistance studies should be emphasized for bioburden based sterilization cycles.

If you are referencing information previously submitted to meet these recommendations, it should include the application number and submission date, and any other relevant citations to the Agency's records where the information can be found.[14]

[13] Knowledge management and quality risk management can be used to continually improve manufacturing capabilities throughout the life cycle for a terminal sterilization program.

[14] See 21 CFR 314.50(g)(1) or 21 CFR 601.2.

B. Risk Assessment, Process Understanding, and Prior Knowledge

Successful parametric release systems are based on the reliability of the control strategy of the sterility assurance program. We recommend that your risk assessment focus on the risk of failure to achieve the minimum required probability of a non-sterile unit for each unit of every batch. The risk assessment should include the following:

- Consistency of performance of the terminal sterilization cycle within the validated limits.
- A discussion of risk to the sterility of the product relative to the following: (1) the production terminal sterilization cycle, (2) the production loading patterns, (3) the container closure system (including secondary packaging), and (4) any potential contamination risks from the environment (as appropriate). For an approved application, you should indicate any changes to the above items and provide an assessment of the risk to the sterility of the product associated with those changes. For example, although the established minimum sterilization time cannot be lowered, the maximum sterilization time can be increased if the appropriate stability data are provided to support the increase.
- Experience with the proposed or similar product (and container closure system) and proposed or similar sterilization process, the overall risks to sterility, and the steps you have taken to assess and control these risks. For new products, prior knowledge from developmental and registration/exhibit batches may suffice.
- A discussion of your overall prior knowledge and production and testing experience relevant to the drug product that will be subject to parametric release.

C. Documentation for Parametric Release Process

The following information specific to the proposed parametric release process should also be included in your submission:

- A citation to a complete and detailed description of the current relevant terminal sterilization cycle.
- Identification of the critical process parameters (process/cycle parameters and appropriate load monitors essential for product release) for the product(s) proposed for parametric release, including the minimum and maximum limits for these critical parameters. The critical process parameters should be within the limits that have been validated and approved for sterility assurance of the subject product(s).
- Acknowledgement that adherence to the critical parameters of the parametric release program will substitute for the performance of a sterility test as the primary release criterion for the product and that sterility test results from the finished product will not be used to overrule any failure to meet the acceptance criteria of the parametric release

program. In the event of failure, the specific sterilizer load will be rejected by the quality control unit and will not be released unless there is a provision for reprocessing.

- Acknowledgement that regardless of the batch release technique used, any specimen tested according to the reference test method for sterility (e.g., compendium or FDA regulations) will meet the criteria for sterility (such as during testing for stability or postmarketing investigations).

- A description of the sterilization load monitor that indicates the following: (1) the type of monitor being proposed, (2) how the load monitor will be used and analyzed, (3) what functions are being measured by the monitor, and (4) the rationale for the location of the monitor. Additionally, for indirect monitors, we recommend that you include a statement justifying the classification of the indirect indicator that you are using as defined by the American National Standard Institute (ANSI 2008). In certain circumstances a Class 3 indicator may be appropriate; however, a Class 5 indicator is recommended for most situations.

- Documentation of the control system to verify exposure of the load to the sterilization process.

- Revision of the certificates of analysis or batch release records for each product subject to parametric release to indicate that parametric release is now the method used to provide assurance of the requirement of sterility. We recommend that you provide a reference to show the link between batch release criteria and the commitments in the application.

IV. FILING REQUIREMENTS

To request parametric release in an original application submission, the request should include information specific to parametric release along with sterilization validation information and product release criteria. For changes to an approved application, the request for parametric release should be submitted in a prior approval supplement under 21 CFR 314.70, 21 CFR 601.12 or 21 CFR 514.8(b)(2). The change to parametric release requires FDA approval before its implementation. If the applicant has current experience using parametric release with a comparable sterilization cycle at the same manufacturing site, and the proposed product's manufacturing process fits into the same validation protocol for parametric release (e.g., container closure system, load patterns, cycle process parameters, and cycle acceptance criteria), then the applicant should meet the filing requirements with a special report for a human drug product,[15] or an annual report for a veterinary drug product[16] or a biologic product.[17] If your product fits into one of these filing categories, contact the review division for your product to verify submission requirements.

[15] 21 CFR 314.81(b)(3)(ii)
[16] 21 CFR 514.8 (b)(4)
[17] 21 CFR 601.12(d)

V. REFERENCES

American National Standard Institute (ANSI), Association for the Advancement of Medical Instrumentation (AAMI), International Organization for Standardization (ISO) 15882, 2008, Sterilization of Health Care Products-Chemical Indicators-Guidance for Selection, Use and Interpretation of Results.

The European Agency for the Evaluation of Medicinal Product (EMEA), 2001; Committee for Proprietary Medicinal Products: Note for Guidance on Parametric Release, March 2001, CPMP/QWP/3015/99.

Food and Drug Administration, 1987, Parametric Release - Terminally Heat Sterilized Drug Products, Compliance Policy Guide (CPG) 460.800 (CPG 7132a.14), October 2, 1987.

International Conference Harmonisation (ICH), 2000, Guidance on Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances, Guidance for Industry, Federal Register, Vol. 65, No. 251, December 29, 2000.

ICH, 2006, Q9 Quality Risk Management, Guidance for Industry, Federal Register, Vol. 71, No. 106, June 2006.

ICH, 2009, Q10 Pharmaceutical Quality System, Guidance for Industry, Federal Register, Vol. 74, No. 66, April 2009.

PDA Journal of Pharmaceutical Science and Technology, Technical Report No. 30: Parametric Release of Pharmaceuticals Terminally Sterilized by Moist Heat, Supplement, Volume 53, Number 4, July-August 1999

Pharmaceutical Inspection Convention/Pharmaceutical Inspection Co-operation Scheme (PIC/S): Guidance on Parametric Release, 2007, PI 005-3, September 25, 2007.

Sasaki, T., 2002, Parametric Release for Moist Heated Pharmaceutical Products in Japan, PDA Journal of GMP and Validation in Japan, Volume 4, Number 1.

United States Pharmacopeia (USP) 32-NF, General Chapter <1222> Terminally Sterilized Pharmaceutical Products-Parametric Release, 2009.