Guidance for Industry

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

DRAFT GUIDANCE

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
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August 2008
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This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic.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 post-marketing 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 biological 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 GMPs 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, and 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] CGMP requirements for process validation are found at 21 CFR 211.100 and, for sterile products in particular at 21 CFR 211.113(b).

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. We recommend discussion with the review division to determine appropriateness of the guidance regarding submission filing and content details.

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: (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 effects of the sterilization process on the product itself, and the microorganisms associated with the product. Parametric release of the batch is then based on documented evidence of the control of critical parameters, removing the need for testing of samples drawn from the finished product.

[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://fda.gov/cder/guidance/index.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://fda.gov/cvm/guidance/published.htm, and CBER guidance documents can be found at http://www.fda.gov/cber/guidelines.htm.

The *sterilization load monitor*,[8] either in the form of a chemical indicator[9] or a biological indicator, is included with each load to demonstrate that the sterilization cycle has occurred and the criteria for critical parameters have been met. The load monitor is placed in an appropriate position in the load, based on the evaluation of development and qualification data. The load monitor can be a direct measurement of lethality delivered to the load, or an indirect lethality measurement system; however, direct measurement is preferred. Either of these approaches can satisfy the CGMP requirement for a laboratory test[10] when used in combination with a sterility assurance program that is in a demonstrated state of control.

FDA conducts scientific evaluation of the parametric release program as part of a cooperative effort between the review staff, compliance staff, and field investigators to ensure the overall state of control of the sterile processing of human and veterinary drug products. Information included in an approved application or supplement is subject to CGMP requirements and inspection.

FDA has accepted the practice of parametric release for products terminally sterilized by moist heat since 1985. Parametric release, described in ICH *Q6A*,[11] is endorsed by regulatory and/or pharmaceutical manufacturing groups in the US, EU, and Japan.[12]

III. CONTENT OF SUBMISSIONS FOR PARAMETRIC RELEASE

An application to FDA is required to obtain approval for parametric release.[13] The approval of parametric release practices is based on an assessment of the applicant's proposed critical process parameters and how they are controlled. As always, adherence to CGMPs is required for marketed products. Demonstrated reliability of the production terminal sterilization cycle, microbiological control and monitoring and control of production cycle parameters within established validated limits is part of this assessment. The specific terminal sterilization process for the product proposed for parametric release should be the same as the process already approved in the application and for original applications, 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.*[14]

FDA approval of the parametric release program will be based on how well the firm has addressed the risks to product sterility. A statement that describes how the risk assessment

[8] See section III. C., bullet 5.
[9] See reference 2 in section V.
[10] See 21 CFR 211.167(a).
[11] ICH *Guidance on Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances*, Federal Register, Vol. 65, No. 251, December 29, 2000. See also footnote 7.
[12] See references 1, 3, and 4 in section V.
[13] 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; 21 CFR 601.2(a) for biological products.
[14] See footnotes 6 and 7.

includes current control strategies for the terminal sterilization cycle, the risk that these strategies might fail to assure sterility, and how prior manufacturing experience and knowledge were incorporated into the risk assessment should be provided in the application.

A. Control Strategy for the Terminal Sterilization Cycle

The control strategy assures that the acceptance criteria of the parametric release process and terminal sterilization cycle are consistently met, thus assuring the sterility of the product. The control strategy should include:

- The rationale for the methods implemented for monitoring and control of the terminal sterilization process used for the product release cycle (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.
- A description of the microbiological monitoring plan for the product and components prior to terminal sterilization, with emphasis on spore detection and heat resistance of bioburden in the product, or a statement that the plan has not changed since last approved and validated.

If you are referencing information previously submitted to meet these recommendations, it should include the identity of the file by name, application number, volume, and page number in the Agency's records where the information can be found.[15]

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 sterility for each unit of every batch. The risk assessment should include:

- Consistency of performance of the terminal sterilization cycle within the approved, validated limits.

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

- A discussion of any changes made to the original submission regarding: 1) the production terminal sterilization cycle (e.g., the established minimum limit cannot be lowered; however, maximum limits can be increased with appropriate stability data to support the increase), 2) the production loading patterns, and 3) the container closure system (including secondary packaging). You should also include an assessment of the risk to sterility associated with these changes.

- Experience with the proposed or similar product (and container closure system), the overall risks to sterility, and the steps you have taken to assess and control these risks.

- 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:

- The application/supplement number(s), including approval date(s), of the submission(s) that provides for the current terminal sterilization cycle, as applicable.

- Identification of the critical process parameters (process/cycle parameters 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 the parametric release system is the primary release test and that test results based on drawing samples from the finished product will not be used to overrule it. In the event of failure to meet the parametric release critical parameter criteria, the specific sterilizer load will be rejected by the quality control unit and will not be released unless there is a provision for resterilization. In such cases, issues of stability and container closure integrity also become relevant.

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

- A description of the sterilization load monitor including indication of: 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 in International Standards Organization (ISO) document 11140 (see section V, reference 2).

- Revision of the certificates of analysis for batch release 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 in the certificate of analysis either a reference to an SOP or a description of the parametric release acceptance criteria 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 can 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 approval before its implementation, unless a different agreement is reached with the FDA (e.g., comparability protocol). If you have current experience using parametric release with the same 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 you can meet the filing requirements with a special report (21 CFR 314.81(b)(3)(ii)) or annual report (21 CFR 514.8 (b)(4)).

V. REFERENCES

1. The European Agency for the Evaluation of Medicinal Product (EMEA); Committee for Proprietary Medicinal Products: Note for Guidance on Parametric Release, February 2001, CPMP/QWP/3015/99. Internet address: http://www.emea.europa.eu

2. International Standards Organization (ISO) 11140. Sterilization of Health Care Products-Chemical Indicators. 2005, ISO, Geneva, Switzerland.

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

4. Pharmaceutical Inspection Convention/Pharmaceutical Inspection Co-operation Scheme (PIC/S): Guidance on Parametric Release, September 2007. Internet address: http://www.picscheme.org.

5. United States Pharmacopeia (USP), General Chapter <71> Sterility Tests.

6. FDA Compliance Policy Guide (CPG) 460.800.