
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DRAFT GUIDANCE

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Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Veterinary Medicine (CVM)
Center for Biologics Evaluation and Research (CBER)**

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1 **Guidance for Industry¹**
2 **Submission of Documentation in Applications for Parametric**
3 **Release of Human and Veterinary Drug Products Terminally**
4 **Sterilized by Moist Heat Processes**
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7 This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current
8 thinking on this topic. It does not create or confer any rights for or on any person and does not operate to
9 bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of
10 the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA
11 staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call
12 the appropriate number listed on the title page of this guidance.
13

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16 **I. INTRODUCTION**
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18 This guidance provides recommendations to applicants on information to include in support of
19 parametric release for sterile products² terminally sterilized by moist heat when submitting a new
20 drug application (NDA), abbreviated new drug application (ANDA), new animal drug
21 application (NADA), abbreviated new animal drug application (ANADA), biologics license
22 application (BLA), or supplement or other post-marketing report.
23

24 Currently, FDA requires that sterile products meet certain sterility requirements before release to
25 the market.^{3, 4} In many cases, the requirements for batch release are fulfilled by conducting a
26 sterility test on finished units drawn from the batch. *Parametric release* is defined as a sterility
27 assurance release program where demonstrated control of the sterilization process enables a firm
28 to use defined critical process controls, in lieu of the sterility test, to fulfill the intent of 21 CFR
29 211.165(a), and 211.167(a).⁵ Under this strategy, market release of terminally sterilized
30 products can be based upon meeting the defined sterilization parameters and not on performing
31 an approved sterility test. Meeting the requirements of the parametric release process can
32 provide greater assurance that a batch meets the sterility requirement than can be achieved with a
33 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.

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35 This guidance does not provide information on procedures, studies, and data concerning efficacy
36 and qualification/validation of moist heat sterilization processes. This guidance also does not
37 provide information on sterility assurance validation programs. However, you may find
38 information relating to such topics in the Agency's guidance for industry on *Submission of*
39 *Documentation for Sterilization Process Validation in Applications for Human and Veterinary*
40 *Drug Products*.^{6, 7} CGMP requirements for process validation are found at 21 CFR 211.100
41 and, for sterile products in particular at 21 CFR 211.113(b).

42

43 The principles in the guidance may also be applicable to products sterilized by other terminal
44 sterilization processes, such as radiation sterilization, which may be suitable for parametric
45 release. We recommend discussion with the review division to determine appropriateness of the
46 guidance regarding submission filing and content details.

47

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

53

II. BACKGROUND

54

55
56 Sterility testing by cultivation of finished units drawn from the batch is limited in its ability to
57 detect contamination because of: (1) the small number of samples required for testing, which
58 restricts the ability to capture those microorganisms dispersed in a large volume, and (2) the
59 limited ability of the prescribed culture media to stimulate growth of all potential
60 microorganisms. Typically, these tests will detect only major errors in the manufacturing
61 process that result in contamination of a large number of product units. However, data derived
62 from in-process controls of a validated terminal sterilization process can provide more accurate
63 information regarding product sterility because the probability of product bioburden surviving
64 the sterilization process in any single unit of a product can be calculated to be less than one in a
65 million.

66

67 Parametric release allows manufacturers to replace sterility testing of samples drawn from the
68 finished product as a release criterion with acceptance criteria for the control of identified
69 process parameters. These parameters, called *critical parameters*, are critical to a successful
70 sterilization process and are based on an in-depth knowledge of the process, the product, the
71 effects of the sterilization process on the product itself, and the microorganisms associated with
72 the product. Parametric release of the batch is then based on documented evidence of the control
73 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>.

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75 The *sterilization load monitor*,⁸ either in the form of a chemical indicator⁹ or a biological
76 indicator, is included with each load to demonstrate that the sterilization cycle has occurred and
77 the criteria for critical parameters have been met. The load monitor is placed in an appropriate
78 position in the load, based on the evaluation of development and qualification data. The load
79 monitor can be a direct measurement of lethality delivered to the load, or an indirect lethality
80 measurement system; however, direct measurement is preferred. Either of these approaches can
81 satisfy the CGMP requirement for a laboratory test¹⁰ when used in combination with a sterility
82 assurance program that is in a demonstrated state of control.

83

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

89

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

93

94 III. CONTENT OF SUBMISSIONS FOR PARAMETRIC RELEASE

95

96 An application to FDA is required to obtain approval for parametric release.¹³ The approval of
97 parametric release practices is based on an assessment of the applicant's proposed critical
98 process parameters and how they are controlled. As always, adherence to CGMPs is required for
99 marketed products. Demonstrated reliability of the production terminal sterilization cycle,
100 microbiological control and monitoring and control of production cycle parameters within
101 established validated limits is part of this assessment. The specific terminal sterilization process
102 for the product proposed for parametric release should be the same as the process already
103 approved in the application and for original applications, validated according to the Agency's
104 guidance for industry on *Submission of Documentation for Sterilization Process Validation in
105 Applications for Human and Veterinary Drug Products*.¹⁴

106

107 FDA approval of the parametric release program will be based on how well the firm has
108 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.

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

112

A. Control Strategy for the Terminal Sterilization Cycle

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

117 The control strategy should include:

118

- 119 • The rationale for the methods implemented for monitoring and control of the terminal
120 sterilization process used for the product release cycle (the critical process parameters).
- 121
- 122 • The rationale for the selection of critical process parameter(s).
- 123
- 124 • A description of the acceptance criteria for parametric release.
- 125
- 126 • A description of the drug product and container closure system (including secondary
127 packaging, as applicable) that will be part of the parametric release program.
- 128
- 129 • A description of the proposed production loading patterns, and verification that they are
130 within the validated limits for the terminal sterilization cycle, or a statement that they
131 have not changed since last approved and validated.
- 132
- 133 • A description of the microbiological monitoring plan for the product and components
134 prior to terminal sterilization, with emphasis on spore detection and heat resistance of
135 bioburden in the product, or a statement that the plan has not changed since last approved
136 and validated.

137

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

141

B. Risk Assessment, Process Understanding, and Prior Knowledge

143

144 Successful parametric release systems are based on the reliability of the control strategy of the
145 sterility assurance program. We recommend that your risk assessment focus on the risk of
146 failure to achieve sterility for each unit of every batch. The risk assessment should include:

147

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

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

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- 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.
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C. Documentation for Parametric Release Process

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163 The following information specific to the proposed parametric release process should also be

164 included in your submission:

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- 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).
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- 194 • Revision of the certificates of analysis for batch release for each product subject to
195 parametric release to indicate that parametric release is now the method used to provide
196 assurance of the requirement of sterility. We recommend that you provide in the
197 certificate of analysis either a reference to an SOP or a description of the parametric
198 release acceptance criteria to show the link between batch release criteria and the
199 commitments in the application.
200

201

IV. FILING REQUIREMENTS

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203
204 To request parametric release in an original application submission, the request should include
205 information specific to parametric release along with sterilization validation information and
206 product release criteria. For changes to an approved application, the request for parametric
207 release can be submitted in a prior approval supplement under 21 CFR 314.70, 21 CFR 601.12,
208 or 21 CFR 514.8(b)(2). The change to parametric release requires approval before its
209 implementation, unless a different agreement is reached with the FDA (e.g., comparability
210 protocol). If you have current experience using parametric release with the same sterilization
211 cycle at the same manufacturing site and the proposed product's manufacturing process fits into
212 the same validation protocol for parametric release (e.g., container closure system, load patterns,
213 cycle process parameters, and cycle acceptance criteria), then you can meet the filing
214 requirements with a special report (21 CFR 314.81(b)(3)(ii)) or annual report (21 CFR 514.8
215 (b)(4)).
216

V. REFERENCES

217

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227 Pharmaceutical Products in Japan, Tsuguo Sasaki, Volume 4, Number 1 (2002).
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230 (PIC/S): Guidance on Parametric Release, September 2007. Internet address:
231 <http://www.picscheme.org>.
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233 5. United States Pharmacopeia (USP), General Chapter <71> Sterility Tests.
234
235 6. FDA Compliance Policy Guide (CPG) 460.800.