
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

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Contains Nonbinding Recommendations

35 This guidance does not provide information on procedures, studies, or 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} Current Good Manufacturing Practices (CGMP) requirements for process
41 validation are found at 21 CFR 211.100 and, for sterile products in particular, at 21 CFR
42 211.113(b). Adherence to CGMPs is required for all marketed products.

43
44 The principles in the guidance may also be applicable to products sterilized by other terminal
45 sterilization processes, such as radiation sterilization, which may be suitable for parametric
46 release. For these types of applications, we recommend the applicant discuss with the review
47 division whether applying the guidance would be appropriate.

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

54 55 **II. BACKGROUND**

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

67
68 Parametric release allows manufacturers to replace sterility testing of samples drawn from the
69 finished product as a release criterion with acceptance criteria for the control of identified
70 process parameters. These parameters, called *critical parameters*, are critical to a successful
71 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>.

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

76
77 A *sterilization load monitor*,⁸ either in the form of a physical, chemical (ANSI 2008), or
78 biological indicator, is included with each load to satisfy the requirement for a laboratory test.⁹
79 In addition, the sterilization load monitor is always considered a critical process parameter. A
80 successful load monitor result, the meeting of the acceptance criteria of the critical parameters,
81 and having a well validated sterility assurance program demonstrate that there is a state of
82 control of the manufacturing process for the product. The load monitor(s) should be placed in
83 appropriate positions to indicate that the load was exposed to a sterilization process which was
84 measured and recorded for conformance with defined criteria for parametric release. This
85 position(s) is determined based on the evaluation of development and qualification data. The
86 location and number of monitors should be described and justified in the application. Alternative
87 procedures for demonstrating that a load or part of a load was exposed to a sterilization process
88 should be discussed with the review division(s) prior to submitting a plan for parametric release.

89
90 FDA conducts scientific evaluation of the parametric release program as part of a cooperative
91 effort among our review staff, compliance staff, and field investigators.

92
93 FDA has accepted the practice of parametric release for drug products terminally sterilized by
94 moist heat since 1985. Parametric release, described in the International Conference on
95 Harmonisation (ICH) Q6A (ICH 2000),¹⁰ is endorsed by regulatory and/or pharmaceutical
96 manufacturing groups in the US (PDA 1999, USP 2009), EU (PIC/S 2007, EMEA 2001), and
97 Japan (Sasaki 2002).

98 99 **III. CONTENT OF SUBMISSIONS FOR PARAMETRIC RELEASE**

100
101 Section IV describes what submissions are required to obtain approval for parametric release.¹¹
102 The approval of parametric release practices is based on an assessment of the applicant's
103 proposed critical process parameters and how they are controlled. Demonstrated reliability of
104 the production terminal sterilization cycle, microbiological control, and monitoring and control
105 of production cycle parameters within established validated limits are part of this assessment.
106 The terminal sterilization process for the product proposed for parametric release should be
107 validated according to the Agency's guidance for industry on *Submission of Documentation for*
108 *Sterilization Process Validation in Applications for Human and Veterinary Drug Products*.¹²
109

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.

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

- 113
- 114 • Current strategies for control of the terminal sterilization program;
- 115
- 116 • Risk that these strategies might fail to ensure sterility; and
- 117
- 118 • How prior manufacturing experience and knowledge were incorporated into the risk
119 assessment.¹³
- 120

A. Control Strategy for the Terminal Sterilization Program

121

122

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

125

126 The control strategy should include the following:

- 127
- 128 • The rationale for the methods implemented to monitor and control the terminal
129 sterilization process used for the product release (the critical process parameters);
- 130
- 131 • The rationale for the selection of critical process parameter(s);
- 132
- 133 • A description of the acceptance criteria for parametric release;
- 134
- 135 • A description of the drug product and container closure system (including secondary
136 packaging, as applicable) that will be part of the parametric release program;
- 137
- 138 • A description of the proposed production loading patterns and verification that they are
139 within the validated limits for the terminal sterilization cycle, or a statement that they
140 have not changed since last approved and validated (as applicable); and
- 141
- 142 • A description of the microbiological monitoring plan for the product and components
143 prior to terminal sterilization or a statement that the plan has not changed since last
144 validated. Spore detection and heat resistance studies should be emphasized for
145 bioburden based sterilization cycles.
- 146

147 If you are referencing information previously submitted to meet these recommendations, it
148 should include the application number and submission date, and any other relevant citations to
149 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.

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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

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

- 194
- 195 • Acknowledgement that regardless of the batch release technique used, any specimen
196 tested according to the reference test method for sterility (e.g., compendium or FDA
197 regulations) will meet the criteria for sterility (such as during testing for stability or
198 postmarketing investigations).
199
- 200 • A description of the sterilization load monitor that indicates the following: (1) the type of
201 monitor being proposed, (2) how the load monitor will be used and analyzed, (3) what
202 functions are being measured by the monitor, and (4) the rationale for the location of the
203 monitor. Additionally, for indirect monitors, we recommend that you include a statement
204 justifying the classification of the indirect indicator that you are using as defined by the
205 American National Standard Institute (ANSI 2008). In certain circumstances a Class 3
206 indicator may be appropriate; however, a Class 5 indicator is recommended for most
207 situations.
208
- 209 • Documentation of the control system to verify exposure of the load to the sterilization
210 process.
211
- 212 • Revision of the certificates of analysis or batch release records for each product subject to
213 parametric release to indicate that parametric release is now the method used to provide
214 assurance of the requirement of sterility. We recommend that you provide a reference to
215 show the link between batch release criteria and the commitments in the application.
216

217 **IV. FILING REQUIREMENTS**

218 To request parametric release in an original application submission, the request should include
219 information specific to parametric release along with sterilization validation information and
220 product release criteria. For changes to an approved application, the request for parametric
221 release should be submitted in a prior approval supplement under 21 CFR 314.70, 21 CFR
222 601.12 or 21 CFR 514.8(b)(2). The change to parametric release requires FDA approval before
223 its implementation. If the applicant has current experience using parametric release with a
224 comparable sterilization cycle at the same manufacturing site, and the proposed product's
225 manufacturing process fits into the same validation protocol for parametric release (e.g.,
226 container closure system, load patterns, cycle process parameters, and cycle acceptance criteria),
227 then the applicant should meet the filing requirements with a special report for a human drug
228 product,¹⁵ or an annual report for a veterinary drug product¹⁶ or a biologic product.¹⁷ If your
229 product fits into one of these filing categories, contact the review division for your product to
230 verify submission requirements.
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¹⁵ 21 CFR 314.81(b)(3)(ii)

¹⁶ 21 CFR 514.8 (b)(4)

¹⁷ 21 CFR 601.12(d)

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234 **V. REFERENCES**

235

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

240

241 The European Agency for the Evaluation of Medicinal Product (EMA), 2001; Committee for
242 Proprietary Medicinal Products: [Note for Guidance on Parametric Release](#), March 2001,
243 CPMP/QWP/3015/99.

244

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

247

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

252

253 ICH, 2006, [Q9 Quality Risk Management](#), Guidance for Industry, Federal Register, Vol. 71, No.
254 106, June 2006.

255

256 ICH, 2009, [Q10 Pharmaceutical Quality System](#), Guidance for Industry, Federal Register, Vol.
257 74, No. 66, April 2009.

258

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

262

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

265

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

268

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