
Setting Endotoxin Limits During Development of Investigational Oncology Drugs and Biological Products Guidance for Industry

DRAFT GUIDANCE

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**U.S. Department of Health and Human Services
Food and Drug Administration
Oncology Center of Excellence (OCE)
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)**

**July 2020
Clinical/Medical**

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1 **Setting Endotoxin Limits During Development of Investigational**
2 **Oncology Drugs and Biological Products**
3 **Guidance for Industry¹**
4
5

6
7 This draft guidance, when finalized, will represent the current thinking of the Food and Drug
8 Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not
9 binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the
10 applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible
11 for this guidance as listed on the title page.
12

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15 **I. INTRODUCTION**
16

17 New approvals in oncology often build on prior success by adding new drugs to current regimens
18 or by combining products in a novel treatment regimen, creating new multidrug regimens² that
19 may have greater efficacy.³
20

21 This guidance describes FDA's recommendations to investigational new drug sponsors for
22 setting endotoxin limits during the development of investigational drugs intended for use in
23 combination with other approved drugs or for the codevelopment of two or more investigational
24 drugs. The scope of this guidance is limited to anticancer drugs, including combination products
25 under 21 CFR Part 3,⁴ as described further in this guidance and administered parenterally (except
26 for intraocular administration) to treat serious and life-threatening cancers based on histology or
27 stage of disease. This guidance does not apply to the development of drugs for adjuvant or
28 neoadjuvant treatment or for cancer subtypes that can be cured or where prolonged survival can
29 be achieved with available therapy.
30

31 In general, FDA's guidance documents do not establish legally enforceable responsibilities.
32 Instead, guidances describe the Agency's current thinking on a topic and should be viewed only
33 as recommendations, unless specific regulatory or statutory requirements are cited. The use of

¹ This guidance has been prepared by the Oncology Center of Excellence in cooperation with the Center for Drug Evaluation and Research and the Center for Biologics Evaluation and Research at the Food and Drug Administration.

² For the purpose of this guidance, *regimen* refers to two or more therapeutic products that are (or will be) marketed separately but are being tested for use in combination based upon one or more adequate and well-controlled trials.

³ See the guidance for industry *Codevelopment of Two or More New Investigational Drugs for Use in Combination* (June 2013). We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA guidance web page at <https://www.fda.gov/regulatory-information/search-fda-guidance-documents>.

⁴ Additional considerations regarding endotoxin exposure may apply for delivery devices and combination products with device constituent parts under 21 CFR 812.

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34 the word *should* in Agency guidances means that something is suggested or recommended but
35 not required.

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II. BACKGROUND

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40 Investigational drugs for treating patients with incurable cancers who have short life expectancy
41 are often studied in combination with approved drugs in an attempt to identify multidrug or
42 multimodality regimens that may prolong survival. Administration of one or more drugs within
43 the same 60-minute time frame as the investigational drug may pose challenges regarding the
44 endotoxin limits for that investigational drug at a time when the manufacturing process for that
45 investigational drug has not been optimized. This guidance addresses endotoxin limits for
46 investigational drugs for the treatment of advanced cancer, when evaluated in early (pilot)
47 clinical trials as part of a multidrug regimen.

48

49 FDA recognizes that based on the potential benefits of investigational drugs administered to
50 patients with life-threatening incurable cancers, such patients' possible exposure to increased
51 levels of endotoxin exceeding the recommendations in USP General Chapter <85> *Bacterial*
52 *Endotoxins Test* may be considered an acceptable risk under appropriate circumstances.

53

54 This guidance discusses FDA's thinking regarding setting endotoxin limits for investigational
55 drugs during early product development for incurable cancers. The recommendations are
56 consistent with the abbreviated product testing for feasibility clinical trials of monoclonal
57 antibodies in patients with serious or immediately life-threatening conditions for which no
58 effective alternative treatment exists.⁵ In this guidance, FDA recommends a risk-based approach,
59 weighing the potential risks of possible exposure to increased levels of endotoxin across all
60 components of a multidrug regimen against the potential benefits to patients with serious and
61 life-threatening cancers.

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63

III. ENDOTOXIN CONTROL AND LIMITS

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66 Bacterial endotoxins are lipopolysaccharides found in the outer membrane of gram-negative
67 bacteria. Endotoxins are released upon cell death and lysis and have the potential to contaminate
68 drug and biological products. When administered in high amounts, endotoxins can cause
69 pyrogenic reactions, severe inflammatory responses, septic shock, and death. Therefore, it is
70 important to prevent the introduction of bacterial endotoxins into drug and biological products
71 and their components (as defined in 21 CFR 201.3) during the product and component
72 manufacturing processes, and to conduct appropriate testing for the presence of endotoxins on
73 each batch of clinical and commercial product. Following are several guidances that refer to the
74 need for pyrogen and endotoxin control and testing during sterile drug and biological product
75 development:

76

⁵ See *Points to Consider in the Manufacture and Testing of Monoclonal Antibody Products for Human Use* (February 1997).

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- 77 • Guidance for industry *Content and Format of Investigational New Drug Applications*
78 *(INDs) for Phase 1 Studies of Drugs, Including Well-Characterized, Therapeutic,*
79 *Biotechnology-derived Products* (November 1995)
80
- 81 • Guidance for industry *INDs for Phase 2 and Phase 3 Studies—Chemistry, Manufacturing,*
82 *and Controls Information* (May 2003)
83
- 84 • Guidance for reviewers and sponsors *Content and Review of Chemistry, Manufacturing,*
85 *and Control (CMC) Information for Human Somatic Cell Therapy Investigational New*
86 *Drug Applications (INDs)* (April 2008)
87
- 88 • Guidance for industry *Chemistry, Manufacturing, and Control (CMC) Information for*
89 *Human Gene Therapy Investigational New Drug Applications (INDs)* (January 2020)
90
- 91 • Guidance for industry *CGMP for Phase 1 Investigational Drugs* (July 2008)
92
93

94 Controls on pyrogen and endotoxins are part of the chemistry, manufacturing, and control
95 information to be included in an investigational new drug, a new drug, or a biologics license
96 application for most drug products (21 CFR 312.23(a)(7)(iv)(b), 21 CFR 314.50(d)(1)(ii)(a), and
97 21 CFR 601.2(a) and (c), respectively). Similarly, current good manufacturing practice
98 regulations also require control of pyrogen for containers and closures (see 21 CFR 211.94(c)
99 and (d) and 21 CFR 600.11(h) and for most drugs (see 21 CFR 211.165(a), 21 CFR 211.167(a),
100 and 21 CFR 610.13(b)). As described in the guidance for industry *Pyrogen and Endotoxins*
101 *Testing: Questions and Answers* (June 2012), the requirement in 21 CFR 610.13 for rabbit
102 pyrogen testing for certain biological products may be waived if a method equivalent to the
103 pyrogen test is demonstrated in accordance with 21 CFR 610.9.⁶
104

105 Controls on pyrogen and endotoxins are part of the chemistry, manufacturing, and control
106 information to be included in an investigational new drug, a new drug, or a biologics license
107 application (see 21 CFR 312.23(a)(7)(iv)(b), 21 CFR 314.50(d)(1)(ii)(a), and 21 CFR 601.2(a)
108 and (c), respectively). Similarly, current good manufacturing practice regulations also require
109 control of pyrogen (see 21 CFR 211.94(c)(d), 21 CFR 211.165(a), 21 CFR 211.167(a), 21 CFR
110 600.11(h), 21 CFR 610.9 (equivalent methods and processes), and 21 CFR 610.13(b)).
111

112 The compendial recommendations for threshold pyrogenic doses of endotoxins for injectable
113 products are based upon the results of human and animal studies demonstrating the deleterious
114 effects of bacterial endotoxins administration. United States Pharmacopeia (USP) General
115 Chapter <151> *Pyrogen Test* provides a test method and acceptance criteria for the absence of
116 pyrogens by measuring febrile reactions to injectable products. The endotoxin limits for
117 parenteral drugs recommended in USP General Chapter <85> *Bacterial Endotoxins Test* are
118 defined by the formula K/M, where K is the threshold pyrogenic dose of endotoxins per kg of

⁶ FDA supports the principles of the 3Rs, to reduce, refine, and replace animal use in testing when feasible. We encourage sponsors to consult with us if they wish to use a nonanimal testing method they believe is suitable, adequate, validated, and feasible. We will consider if the alternative method could be assessed for equivalency to an animal test method.

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119 body weight or m^2 of body surface area per hour and M is the maximum dose to be administered
120 to the patient within a 60-minute period. K is equal to 5 EU (endotoxin units) per kg of body
121 weight or 100 EU per m^2 of body surface area per hour for nonintrathecal injections. K is equal
122 to 0.2 EU per kg of body weight per hour for intrathecal injections. These compendial
123 recommendations represent the upper limit for endotoxin content for injectable products so
124 stricter limits may be warranted.

125
126 These values represent the maximum recommended exposure to endotoxins, based on the
127 absence of clinically important increases in body temperature at these exposures. FDA expects
128 that sponsors of investigational new drug applications will justify the proposed endotoxin
129 acceptance criteria for each investigational therapeutic biologic, drug, or combination therapy
130 based on manufacturing experience and established control strategies, such as careful selection
131 of ancillary materials, aseptic processing, and the use of closed systems.

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133

IV. SETTING ENDOTOXIN LIMITS DURING DRUG DEVELOPMENT

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136 In keeping with the principles of facilitating drug development for serious and life-threatening
137 diseases, this guidance outlines FDA's current thinking on a risk-based approach to setting
138 acceptance criteria for endotoxins during the clinical development of drugs intended to treat
139 serious and life-threatening cancers. Additionally, sponsors should refer to recommendations
140 regarding testing discussed in the guidance for industry *Pyrogen and Endotoxins Testing:
141 Questions and Answers*.

142

A. Early Clinical Development

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144

145 During early clinical trials (e.g., dose-finding or activity-estimating trials) conducted in patients
146 with a serious and life-threatening cancer based on stage of disease and expected prognosis for
147 that cancer subtype:

148

1. Parenteral (Excluding Intrathecal or Intraocular) Route of Administration

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150

- 151 • For investigational products that are small molecules or certain therapeutic biological
152 products,⁷ the endotoxin limits of an investigational drug or the combined endotoxin
153 limits of multiple investigational drugs administered concomitantly by a parenteral route
154 should not exceed the limit specified in USP General Chapter <85>, that is, 5 USP-EU
155 per kg body weight per hour or 100 EU per m^2 body surface area (BSA) per hour. The
156 sponsor of an investigational new drug need not consider the potential endotoxin
157 contribution from approved and/or licensed components of a combination regimen when
158 calculating the acceptable limits for endotoxin exposure from the investigational drug.
- 159
160 • For all other investigational products, including cellular therapy and gene therapy
161 products, in order to assess causality of observed adverse events, the combined endotoxin
162 exposure from all agents (investigational drug and other approved and/or licensed

⁷ See *Transfer of Therapeutic Products to the Center for Drug Evaluation and Research (CDER)* at <https://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CBER/ucm133463.htm>.

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163 concomitantly administered drugs) administered parenterally should not exceed the limits
164 specified in USP General Chapter <85>; this will allow better identification of adverse
165 reactions of investigational products that may overlap with the onset of and mimic the
166 signs and symptoms of endotoxin exposure.

2. Intrathecal Route of Administration

169
170 When investigational products will be administered intrathecally with other agents, the combined
171 endotoxin exposure from all drugs (investigational drug and other concomitantly administered
172 investigational, approved, or licensed drugs) should not exceed that specified in USP General
173 Chapter <85>, that is, 0.2 USP-EU per kg body weight per hour.

- 174
175 • In the rare case that the combined endotoxin exposure exceeds the limits described above,
176 sponsors should justify that such limits cannot be achieved based on specific aspects of
177 product manufacturing and provide a rationale to support a conclusion that the risks to
178 human subjects are reasonable considering the preliminary evidence of clinical activity of
179 the investigational product, the seriousness of the disease, and the availability of
180 satisfactory alternative therapies.

B. Late Stage Clinical Development

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183
184
185 During clinical trials intended to support the approval of an investigational drug to be
186 administered concomitantly with other drugs:

- 187
188 • Sponsors should tighten the specifications for endotoxin limits to ensure that by the time
189 they submit a marketing application for that drug, the endotoxin limits will not exceed
190 that specified in USP General Chapter <85> for a parenterally administered drug
191 considering the combined endotoxin exposure of the investigational drug and all
192 concomitantly administered drugs cited in the INDICATIONS AND USAGE section of
193 product labeling.

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