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

Guidance for Industry

DRAFT GUIDANCE

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For questions regarding this draft document, contact (CDER) Patricia Keegan at 301-796-1387, or (CBER) Office of Communication, Outreach and Development at 800-835-4709 or 240-402-8010.

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This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic.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

I. INTRODUCTION

New approvals in oncology often build on prior success by adding new drugs to current regimens or by combining products in a novel treatment regimen, creating new multidrug regimens[2] that may have greater efficacy.[3]

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

In general, FDA's guidance documents 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

[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.

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

II. BACKGROUND

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

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

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

III. ENDOTOXIN CONTROL AND LIMITS

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

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

- Guidance for industry *Content and Format of Investigational New Drug Applications (INDs) for Phase 1 Studies of Drugs, Including Well-Characterized, Therapeutic, Biotechnology-derived Products* (November 1995)

- Guidance for industry *INDs for Phase 2 and Phase 3 Studies–Chemistry, Manufacturing, and Controls Information* (May 2003)

- Guidance for reviewers and sponsors *Content and Review of Chemistry, Manufacturing, and Control (CMC) Information for Human Somatic Cell Therapy Investigational New Drug Applications (INDs)* (April 2008)

- Guidance for industry *Chemistry, Manufacturing, and Control (CMC) Information for Human Gene Therapy Investigational New Drug Applications (INDs)* (January 2020)

- Guidance for industry *CGMP for Phase 1 Investigational Drugs* (July 2008)

Controls on pyrogen and endotoxins are part of the chemistry, manufacturing, and control information to be included in an investigational new drug, a new drug, or a biologics license application for most drug products (21 CFR 312.23(a)(7)(iv)(b), 21 CFR 314.50(d)(1)(ii)(a), and 21 CFR 601.2(a) and (c), respectively). Similarly, current good manufacturing practice regulations also require control of pyrogen for containers and closures (see 21 CFR 211.94(c) and (d) and 21 CFR 600.11(h) and for most drugs (see 21 CFR 211.165(a), 21 CFR 211.167(a), and 21 CFR 610.13(b)). As described in the guidance for industry *Pyrogen and Endotoxins Testing: Questions and Answers* (June 2012), the requirement in 21 CFR 610.13 for rabbit pyrogen testing for certain biological products may be waived if a method equivalent to the pyrogen test is demonstrated in accordance with 21 CFR 610.9.[6]

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

The compendial recommendations for threshold pyrogenic doses of endotoxins for injectable products are based upon the results of human and animal studies demonstrating the deleterious effects of bacterial endotoxins administration. United States Pharmacopeia (USP) General Chapter <151> *Pyrogen Test* provides a test method and acceptance criteria for the absence of pyrogens by measuring febrile reactions to injectable products. The endotoxin limits for parenteral drugs recommended in USP General Chapter <85> *Bacterial Endotoxins Test* are 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.

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

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

IV. SETTING ENDOTOXIN LIMITS DURING DRUG DEVELOPMENT

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

A. Early Clinical Development

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

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

- For investigational products that are small molecules or certain therapeutic biological products,[7] the endotoxin limits of an investigational drug or the combined endotoxin limits of multiple investigational drugs administered concomitantly by a parenteral route should not exceed the limit specified in USP General Chapter <85>, that is, 5 USP-EU per kg body weight per hour or 100 EU per m^2 body surface area (BSA) per hour. The sponsor of an investigational new drug need not consider the potential endotoxin contribution from approved and/or licensed components of a combination regimen when calculating the acceptable limits for endotoxin exposure from the investigational drug.

- For all other investigational products, including cellular therapy and gene therapy products, in order to assess causality of observed adverse events, the combined endotoxin 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.

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

2. Intrathecal Route of Administration

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

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

B. Late Stage Clinical Development

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

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

REFERENCES

Burrell R, Human Responses to Bacterial Endotoxin, 1994, Circ Shock, 43:137–153.

Hochstein HD, EA Fitzgerald, FG McMahon, and R Vargas, 1994, Properties of US Standard Endotoxin (EC-5) in Human Male Volunteers. J Endotoxin Res, 1(1):52–56.

Reeve AJ, S Patel, A Fox, K Walker, and L Urban, 2000, Intrathecally Administered Endotoxin or Cytokines Produce Allodynia, Hyperalgesia and Changes in Spinal Cord Neuronal Responses to Nociceptive Stimuli in the Rat, Eur J Pain, 4(3):247–257.

Simmons RL, TB Ducker, and AM Martin Jr., 1969, Comparative Pathology after Intrathecal Endotoxin in the Rabbit, Dog, and Monkey. Experentia, 25(6):622–623.

Suffredini AF, RE Fromm, MM Parker, M Brenner, JA Kovacs, RA Wesley, and JE Parrillo, 1989, The Cardiovascular Response of Normal Humans to the Administration of Endotoxin, N Engl J Med, 321(5):280–287.

Suffredini AF and RJ Noveck, Human Endotoxin Administration as an Experimental Model in Drug Development, 2014, Clin Pharmacol Ther, 96(4):418–422.