
Guidance for Industry Antibacterial Drug Products: Use of Noninferiority Trials to Support Approval

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

**November 2010
Clinical/Antimicrobial**

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Guidance for Industry¹

Antibacterial Drug Products: Use of Noninferiority Trials to Support Approval

This guidance represents 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

The purpose of this guidance is to inform industry of the Food and Drug Administration's (FDA's) current thinking regarding appropriate clinical trial designs to evaluate antibacterial drug products, and to provide an opportunity for sponsors to amend ongoing or completed trials accordingly. This guidance is in response to a number of public discussions in recent years regarding the use of active-controlled trials designed to show noninferiority (NI) as a basis for approval of antimicrobial drug products. These discussions initially focused on the indications acute bacterial sinusitis (ABS), acute bacterial exacerbation of chronic bronchitis (ABECB), and acute bacterial otitis media (ABOM). However, the science of active-controlled trials designed to show NI and the selection of appropriate NI margins in circumstances where an active-controlled trial designed to show NI is an appropriate trial design has been a focus of recent discussions in other antimicrobial drug product indications and in other therapeutic areas as well.²

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

¹ This guidance has been prepared by the Office of Antimicrobial Products, representing the Division of Anti-Infective and Ophthalmology Products and the Division of Special Pathogen and Transplant Products, in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration.

² See the draft guidance for industry *Non-Inferiority Clinical Trials*. When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA Drugs guidance Web page at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>.

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cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

There have been public discussions on the use of NI clinical trial designs for antibacterial drug products at the Anti-Infective Drugs Advisory Committee meetings and workshops sponsored or co-sponsored by the FDA. Based on these deliberations and a review of available data for ABS, ABECB,³ and ABOM, the FDA has not found it possible to define an NI margin for active-controlled NI trials in these three infectious disease therapeutic areas because a consistent and reliable estimate of the efficacy of active treatment relative to placebo has not been established.

These public discussions have contributed to the FDA's evolving understanding of the science of clinical trials and, in particular, the appropriate role of active-controlled trials designed to show NI in the development of antibacterial drug products. We anticipate that continued discussions on the role of active-controlled trials designed to show NI will provide further advancement in the field with regard to the use of NI trials. The draft guidance for industry *Non-Inferiority Clinical Trials* contains general guidance on the use of NI trials and provides more specific methodological advice. Sponsors also should review the ICH guidance for industry *E10 Choice of Control Group and Related Issues in Clinical Trials*,⁴ which provides a general discussion on the selection of control groups, including consideration of conditions under which active-controlled trials designed to show NI can be informative.

For some other infectious disease therapeutic indications (generally for more serious infections, such as hospital-acquired bacterial pneumonia/ventilator-associated bacterial pneumonia, community-acquired bacterial pneumonia, and acute bacterial skin and skin structure infections), available data and deliberations make it possible to define a consistent and reliable estimate of the efficacy of active treatment relative to placebo to serve as the basis for defining a new inferiority margin for an active-controlled NI trial.⁵

³ Patients enrolled in ABECB trials in new drug applications have, in general, included patients with outpatient, milder, or less well-characterized disease.

⁴ We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs guidance Web page at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>.

⁵ For links to transcripts from recent FDA-sponsored or co-sponsored workshops, see the Meetings, Conferences, & Workshops (Drugs) Web site at <http://www.fda.gov/Drugs/NewsEvents/ucm132703.htm>; and for links to transcripts from Anti-Infective Drugs Advisory Committee meetings, see the Advisory Committee Calendar Web site at <http://www.fda.gov/AdvisoryCommittees/Calendar/default.htm>.

III. PROVIDING EVIDENCE TO SUPPORT JUSTIFICATION FOR ACTIVE-CONTROLLED TRIALS DESIGNED TO SHOW NONINFERIORITY

A. Trials Proposed During Protocol Development

We encourage sponsors contemplating use of an active-controlled NI trial design to consider the basis for estimating the treatment effect of a potential active control that will be a critical component of choosing the NI margin as early as possible. This effect is usually estimated from previously conducted trials, but other available information can also be useful. NI trial designs are appropriate only when there is adequate evidence of a defined effect size for the control treatment so that the proposed NI margin can be supported. The time point of the assessment of the efficacy endpoint in the previous trials used to estimate the treatment effect is an important consideration for a proposed NI margin and NI trial design. For an NI trial to be informative, it is critical to have an adequately justified NI margin and to use appropriate efficacy endpoints. If NI trials are being considered, a comprehensive synthesis of the evidence that supports the effect size of the active-control drug product and the proposed NI margin should be assembled during the period of protocol development and provided to the FDA along with the protocol. For any indication being studied using active-controlled trials designed to show NI, sponsors must provide adequate evidence to support the proposed NI margin (21 CFR 314.126).

Any sponsor submitting a protocol for an NI trial under a special protocol assessment (SPA) should provide the evidence to support the choice of an NI margin and the choice of primary efficacy endpoints. It should be recognized, however, that for some indications with a high rate of resolution without antibacterial drug therapy, such as ABS, ABECB,⁶ and ABOM, available data will not support the use of an NI design, and other trial designs (i.e., superiority designs) will be needed to provide evidence of effectiveness in these three indications.⁷ In some cases, it may be useful to compare time for clinical improvement in addition to overall cure rates (e.g., for a demonstration of superiority of the test drug to placebo, to an active control, or to delayed initiation of the test drug or an active control).

B. Ongoing or Completed Trials Intended for Submission to a New Drug Application

Sponsors should re-evaluate all ongoing or completed NI trials that will be submitted in a new drug application for antibacterial indications to ensure that there is an adequate scientific basis for the established effect size of the active control and the proposed NI margin. This

⁶ Patients enrolled in ABECB trials in new drug applications have, in general, included patients with outpatient, milder, or less well-characterized disease.

⁷ See the draft guidances for industry *Acute Bacterial Sinusitis — Developing Drugs for Treatment*, *Acute Bacterial Exacerbations of Chronic Bronchitis in Patients With Chronic Obstructive Pulmonary Disease: Developing Antimicrobial Drugs for Treatment*, and *Acute Bacterial Otitis Media: Developing Drugs for Treatment*. When final, these guidances will represent the FDA's current thinking on these topics. For the most recent version of a guidance, check the FDA Drugs guidance Web page at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>.

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recommendation applies to trials that may have been previously reviewed by the Office of Antimicrobial Products under an SPA. If substantial scientific issues essential to determining the safety or efficacy of the drug have been identified for the NI trial design used, commitments from the FDA under an SPA may no longer be valid.⁸

If the sponsor concludes that an NI design was appropriate for a completed trial or remains appropriate for an ongoing trial, the relevant investigational new drug application (IND) should be amended as soon as possible with the scientific evidence and rationale to support the proposed NI margin. If scientific evidence does not support the proposed NI margin, additional trials employing other designs (e.g., superiority designs) should be considered to provide evidence of effectiveness for the proposed indication. Proposals for additional trials should be submitted to the FDA. See ICH E10 for a discussion on the issues of choice of control group for clinical trials.

Any changes to a sponsor's development program that result from the recommendations in this guidance should be made as early as possible and documented in the sponsor's IND. Sponsors who have questions or who are unsure about the status of their development plans should submit a meeting request to discuss these issues further with the appropriate review division. Alternatively, sponsors should submit a new protocol as part of an SPA, or request a new SPA for a previously reviewed SPA.

⁸ See the guidance for industry *Special Protocol Assessment*.