Guidance for Industry

Antibacterial Drug Products: Use of Noninferiority Studies to Support Approval

DRAFT GUIDANCE

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For questions regarding this draft document contact Edward Cox at 301-796-1300.

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

October 2007
Clinical Antimicrobial

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Division of Drug Information, HFD-240
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857
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TABLE OF CONTENTS

Guidance for Industry[1]
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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 study designs to evaluate antibacterial drugs, and to ask sponsors to amend ongoing or completed studies accordingly. This guidance is in response to a number of public discussions in recent years regarding the use of active-controlled studies designed to show noninferiority (NI) as a basis for approval of antimicrobial drug products (references to the individual meetings can be found in section II, Background). These discussions have focused primarily on the indications acute bacterial sinusitis (ABS), acute bacterial exacerbation of chronic bronchitis (ABECB), and acute bacterial otitis media (ABOM). In addition to the discussions in these three therapeutic areas, the broader question of the role of active-controlled studies designed to show NI to support approval of antimicrobial drugs and the selection of appropriate NI margins (in circumstances where an active-controlled trial designed to show NI is an appropriate trial design) have been issues of recent concern.

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

[1] This guidance has been prepared by the Office of Antimicrobial Products, representing the Division of Anti-Infective and Ophthalmologic 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.

II. BACKGROUND

In October 2003 and September 2006, the Anti-Infective Drugs Advisory Committee (AIDAC) discussed ABS clinical trials, with a focus on the use of NI designs.[2] In September 2006, the AIDAC addressed appropriate use of NI studies for ABS in the context of a specific product.[3] Based on these deliberations and a review of available data, the FDA has not found it possible to define an NI margin for active-controlled NI studies in ABS because a consistent and reliable estimate of the efficacy of active treatment relative to placebo has not been established.

More recently, in a December 2006 joint meeting of the AIDAC and the Drug Safety and Risk Management Advisory Committee, the issue of NI study design was discussed in the context of evaluating the risk-benefit profile of a drug. In this case, ABS, ABECB, and community-acquired pneumonia were the indications under discussion.[4]

Trial designs for the ABOM and ABECB indications and some of the issues with interpretation of trials designed to show NI have been discussed at previous FDA advisory committee meetings; ABOM was discussed on July 11, 2002, and ABECB was part of a broader discussion of NI trial design held on February 19, 2002.[5]

All of 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 studies designed to show NI in the development of antibacterial 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 studies. The FDA plans to publish more general guidance on the use of NI trials to support approval in all therapeutic areas, and will provide more specific methodological advice. Sponsors also should review the ICH guidance for industry *E10 Choice of Control Group and Related Issues in Clinical Trials*,[6] which provides a general discussion on the selection of control groups, including consideration of conditions under which active-controlled studies designed to show NI can be informative.

In addition, it is essential to note that in any proposed trials, adequate provisions need to be in place so that human subjects will not be exposed to an unreasonable and significant risk of illness or injury (21 CFR 312.42). During protocol development, study designs should be carefully considered to ensure that there are adequate provisions to protect patient safety.

[2] See http://www.fda.gov/ohrms/dockets/ac/cder03.html#Anti-Infective and http://www.fda.gov/ohrms/dockets/ac/cder06.html#AntiInfective, respectively.

[3] See http://www.fda.gov/ohrms/dockets/ac/cder06.html#AntiInfective.

[4] See http://www.fda.gov/ohrms/dockets/ac/cder06.html#AntiInfective.

[5] See http://www.fda.gov/ohrms/dockets/ac/cder02.htm#Anti-Infective.

[6] We update guidances periodically. To make sure you have the most recent version of a guidance, check the CDER guidance Web page at http://www.fda.gov/cder/guidance/index.htm.

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

A. Studies Proposed during Protocol Development

We encourage sponsors to carefully consider the basis for demonstrating treatment effect with a particular trial design during protocol development. NI study designs may be appropriate when there is adequate evidence of a defined effect size for the control treatment so that the proposed NI margin can be supported. For an NI study, having an adequately justified NI margin is essential to having an informative study. If NI studies are being considered, a comprehensive synthesis of the evidence that supports the effect size of the active control and the proposed NI margin should be assembled during the period of protocol development and provided to the FDA along with the protocol. We are asking sponsors to provide adequate evidence to support the proposed NI margin for any indication being studied using active-controlled studies designed to show NI (21 CFR 314.126). It is likely, however, that for some indications, such as ABS, ABOM, and ABECB, available data will not support the use of an NI design.[7] We recommend that sponsors consider other study designs (e.g., superiority designs) to provide evidence of effectiveness in these three indications. In some cases, it may be useful to compare time for clinical improvement in addition to overall cure rates.

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

Sponsors should re-evaluate all ongoing or completed NI studies that will be submitted to a new drug application for antibacterial indications to ensure there is adequate scientific rationale for the effect size of the active control and the proposed NI margin that is used. This recommendation includes trials that may have been previously reviewed by the Office of Antimicrobial Products under a special protocol assessment (SPA). Because the state of the science has changed, prior commitments from the FDA under an SPA may no longer be valid for some products.

If the sponsor concludes that an NI study design was appropriate for a completed trial or remains appropriate for an ongoing study, 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 studies employing other study designs (e.g., superiority designs) should be considered to provide evidence of effectiveness for the proposed indication. Proposals for additional studies 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.

[7] Patients enrolled in ABECB studies in new drug applications have, in general, included patients with outpatient, *milder*, or less well-characterized disease.

Alternatively, sponsors should submit a new protocol as part of an SPA, or request a new SPA for a previously reviewed SPA.