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## FDA Issues New Guidance Document on Non-Inferiority Clinical Trials

On March 1, 2010, the Food & Drug Administration (FDA or “the Agency”) issued a draft guidance document entitled “Guidance for Industry: Non-Inferiority Clinical Trials” (“Guidance”).<sup>1</sup>

- The Guidance provides insight into the FDA’s “interpretation of the underlying principles involved in the use of non-inferiority (NI) study designs to provide evidence of the effectiveness of a drug or therapeutic biologic product.”
- It provides detailed advice regarding the selection of the non-inferiority margin (NI margin) that will determine the success or failure of the clinical trial.
- It provides FDA’s current thinking regarding those situations in which a completed NI study may not be interpretable and it explains the Agency’s heightened attention on good study quality and “perverse incentives” in a NI trial.
- Although the Guidance was issued by the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER), it may be instructive for device manufacturers that contemplate the use of NI studies.

**Selection of the non-inferiority margin.** FDA emphasizes that the goal of a NI study “is to show that the difference between the new and active control treatment [*e.g.*, an already-marketed drug or biologic] is small, small enough to allow the known effectiveness of the active control to support the conclusion that the new test drug [or biologic] is also effective.” The guidance clarifies that selection of a NI margin requires two major steps. First, the margin ( $M_1$ ) that defines the “entire effect of the active control assumed to be present in the NI study” must be calculated. This is determined using the historical treatment effect of the active control drug versus placebo that was demonstrated in the statistical analysis of a prior clinical trial. Next, the “**clinical margin**” ( $M_2$ ), which is “the largest clinically acceptable difference (degree of inferiority) of the test drug compared to the active control,” must be selected.  $M_2$  is a subset of  $M_1$  and cannot be greater than  $M_1$ . It is important to note that “ $M_1$  is not measured in the NI trial” and its calculation relies on external information.  $M_1$  is calculated using the historical treatment



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effect of the active control drug, and its robustness depends on the “constancy assumption” that the contemporary effect of the active control drug is similar to the past effect in the historical clinical trial. This risk element in a non-inferiority trial is discussed in more detail below.  $M_2$ , on the other hand, is a more subjective clinical judgment about how much of  $M_1$  should be preserved, or put another way, how much of the effectiveness of the active control is permitted to be lost in the performance of the test drug. The Guidance provides detailed advice on the selection of both  $M_1$  and  $M_2$ , as well as on the statistical methods used to analyze whether the NI objective has been met.

- *As an illustrative example, if the clinical margin ( $M_2$ ) were chosen to be 40% of  $M_1$ , a “successful” clinical trial would mean that there is reasonable assurance that the test drug preserves 60% of the effectiveness of the active control drug but that as much as 40% of its benefit may be lost. It does not mean that the effectiveness of the test drug is “equivalent” or the “same” as the active control drug.*

The Guidance is organized in four parts: (1) a discussion of regulatory, study design, scientific, and statistical issues related to NI studies when used to establish effectiveness of a drug or biologic; (2) a detailed discussion of selected issues, with a particular focus on the NI margins and the techniques used to select the appropriate NI margin; (3) common questions regarding NI studies with accompanying answers and advice; and (4) five examples of selecting NI margins and conducting NI studies.

FDA’s concerns about NI studies, and the need for issuance of the Guidance, spring largely from the fact that NI studies do not stand alone as proof of effectiveness because they lack an active comparison with a placebo or no-treatment control group.

- **Reliance on historical data.** Instead, they require information external to the study (*i.e.*, reference to prior proof of effectiveness of the active control against a placebo in historical clinical trials) in order to properly plan the study’s design and interpret the results (*i.e.*, a finding that the test drug or biologic is not inferior to the active control). *The historical magnitude of effectiveness of the active control in comparison with placebo is critical for determining the NI margin ( $M_1$ ); i.e., the estimation of the effect that the active comparator would have shown versus a placebo had there been a placebo group in the NI study.*<sup>2</sup>
- **Assumption of constancy.** In the absence of a placebo comparison, FDA emphasizes its concern that a NI study always requires major assumptions that the effect of the active control product is “constant” such that it is still actually effective in the context of the NI study. Put simply, a statistical finding that the test product is not inferior to the active control is meaningless from a clinical and regulatory standpoint if there is concern that the magnitude of effectiveness of the active control versus placebo has changed over time. This is a particular concern when there has been substantial evolution over time in the definition of the disease state and/or background medical treatments.
- **Risk that a completed NI study is not interpretable.** FDA warns manufacturers that it may not be possible to assume that the effect of the active comparator is “constant” until the NI study is completed and the similarities of the study population and response to the active control can be evaluated relative to the historical trials in which the active comparator was shown to be superior to placebo. *Thus, any agreement with FDA regarding the choice of the NI margin and the statistical plan does not ensure that FDA will regard the study as interpretable when it is actually completed.*



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**Ethical issues.** Despite these problems with NI studies, FDA notes that there are instances in which NI studies are preferred over superiority studies comparing the test drug or biologic against a placebo or no-treatment control. This is typically the case when there is “an effective treatment that provides an important benefit” already available to patients; assigning patients to a placebo or a no-treatment control group would deny them this available, important benefit and to do so would be unethical. Therefore NI studies are occasionally necessary, even if they are not as conclusive or efficient as superiority studies.

**FDA’s concern about perverse incentives.** In the Guidance, FDA worries that NI studies are especially vulnerable to poor study quality and that there can be perverse incentives that drive NI study design:

“[I]t should be recognized that although most investigators seek to carry out high quality trials, the incentives in an NI study are perverse, and quite different from those in superiority trials. In a superiority trial, sloppiness can lead to study failure, and major efforts in trial conduct and monitoring are therefore devoted to avoiding it. In general, sloppiness of any sort obscures true treatment differences. In an NI trial, in contrast, where the goal is to show no difference (or no difference greater than [the margin]), poor quality can sometimes lead to an apparent finding of non-inferiority that is incorrect. There is therefore a critical need for particular attention to study quality and conduct when planning and executing an NI study.”

The Guidance provides detailed information about the design, statistical analysis, and conduct of NI studies in an attempt to counteract these “perverse” incentives.

**Implications for use of NI studies for medical device manufacturers.** The principles of NI clinical studies elucidated in the Guidance may be relevant for medical device manufacturers who are considering the design of clinical trials. In the context of FDA’s current thinking about NI studies, the absence of prior demonstration of clinical effectiveness of a comparator device could present a major challenge in the use of NI clinical trial design, particularly when used to support 510(k) submissions.

Comments on the Guidance should be submitted to FDA by June 1, 2010.<sup>3</sup> King & Spalding will continue to monitor FDA statements and documents related to non-inferiority studies, as well as clinical trials in general.

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*This alert provides a general summary of recent legal developments. It is not intended to be and should not be relied upon as legal advice.*

<sup>1</sup> 75 Fed. Reg. 9228 (Mar. 1, 2010). The Non-Inferiority Guidance is available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM202140.pdf>.

<sup>2</sup> Depending on the question to be asked in the study, relevant historical clinical trials could include comparison of the active control drug with placebo, a no-treatment control, or a very low dose of the test drug.

<sup>3</sup> Electronic comments may be submitted to <http://www.regulations.gov>.