Latest FDA Guidance on Non-inferiority Designs

To obtain drug approval from the US Food and Drug Administration (FDA), manufacturers must establish efficacy by providing "substantial evidence" of effectiveness from "adequate and well-controlled studies." As stated in 21 Code of Federal Regulations (CFR) 314.126, there are four types of concurrently controlled trials that provide evidence of effectiveness; one of these is the non-inferiority (NI) design, which is typically used when it is not ethical for a trial to include a placebo arm.

In November 2016, the FDA issued a final guidance for industry, *Non-Inferiority Clinical Trials to Establish Effectiveness*, to provide advice on the appropriate use of NI study designs for investigational drugs or biologics. This document finalises the 2010 draft guidance, *Non-Inferiority Clinical Trials* and supersedes the 2010 guidance for industry, *Antibacterial Drug Products: Use of Noninferiority Trials to Support Approval*, which will be withdrawn.

Extensive changes have been made to the current guidance; these include additional recommendations on how to choose an NI margin and when NI trials can provide interpretable results, and detailed discussion on the choice of statistical tests for the NI hypothesis. Other additional information concerns statistical inference, statistical uncertainties, and quantification of the active control effect.

Another noteworthy change in the latest guidance is the inclusion of a new example under the Appendix section, "Determination of an NI margin for Community-Acquired Bacterial Pneumonia (CABP) When No Historical Trials Are Available." This entry replaces former example 2, "The Determination of a Non-Inferiority Margin for Complicated Urinary Tract Infection (cUTI)—Fixed Margin Approach."

As explained in the November 2016 guidance, an NI study seeks to show that the amount by which a test drug is inferior to an active control is less than some pre-specified NI margin (M). M can be no larger than the presumed entire effect of the active control in the NI study, and the margin based on the entire active control effect is generally referred to as M_1. The FDA emphasises that M_1 is not measured in the NI trial (in the absence of a placebo arm), but rather is estimated based on past performance of the active control. The effect is assumed

to be present in the current study based on a thorough comparison of the characteristics of the current NI study with those of prior studies and an assessment of the quality of the NI study.

With the CABP example, the FDA illustrates the point of determining the NI margin using observational data when randomised, placebo-controlled trials of active control drugs are lacking. The example cites a revised draft guidance for developing CABP treatments, issued in 2014, which describes in detail the justification for NI margins with respect to two endpoints: clinical response and mortality. Historical data from three published, non-randomised studies of bacteremic and non-bacteremic patients with pneumococcal or lobar pneumonia were evaluated to justify NI margins for use in future CABP studies.

The FDA points out two limitations in the use of these data to determine an NI margin: 1) only observational data are presented and 2) no recent studies were available, with the most current dating to the 1960s. The agency explains that significant improvements in the standard of care and the availability of improved treatment options for CABP patients compared to the pre-antibiotic era bring into question the relevance of these historical studies for estimating an active control effect on mortality.

Despite the data limitations, the mortality rates among the treated patient cohorts are reasonably consistent (from 5 % to 17 %) across the three decades represented, the FDA notes. Mortality rates in the untreated cohorts are more variable. The older references provide estimates of 31 % and 41 %, while the more recent study gives an estimated mortality rate of 82 %; this estimate, however, is based on a very small sample size (N = 17).

Given the absence of any placebo-controlled trials of active control drugs in CABP, it is not possible to estimate M_1 using the methods advocated in this latest guidance document, according to the FDA. Still, it is clear that the untreated mortality is substantial. For this reason, the agency continues, it is reasonable to assume that the mortality rate due to CABP, if left untreated, will be substantially higher than the rates observed among the treated cohorts, based on the historical evidence described and the caveats noted about the nature and age of the studies.

The FDA concludes in the CABP example that the use of an NI margin of approximately 10 % is a valid approach for evaluating new CABP treatments and would clearly represent an effect superior to no treatment as well as, based on clinical judgment, an appropriate clinical margin.

Comments on the November 2016 guidance document may be submitted to the FDA at any time to Docket No. FDA-2010-D-0075.

The FDA has covered the topic of clinical trial design in relation to CABP at various public meetings, including:

- November 4, 2016: The Antimicrobial Drugs Advisory Committee (AMDAC) considered two new drug applications (NDAs) sponsored by Cempra Pharmaceuticals, Inc for the use of Solithera (solithromycin capsules and solithromycin for injection) to treat CABP. The clinical development programme involved an NI design.
- November 3, 2011: The Anti-Infective Drugs Advisory Committee (AIDAC) discussed design issues for clinical trials of antibacterials to treat CABP, and particularly the issues addressed in the FDA's 2009 draft guidance, *Community-Acquired Bacterial Pneumonia: Developing Drugs for Treatment* (now outdated).
- December 9, 2009: The AIDAC discussed endpoints and other clinical trial design issues for CABP product development.
- April 1-2, 2008: The AIDAC discussed clinical trial design—specifically NI design—for products intended to treat community-acquired pneumonia (CAP).
- January 17-18, 2008: A workshop was co-sponsored by the FDA and the Infectious Diseases Society of America (IDSA) to consider issues in the design and conduct of clinical trials of antibacterial drugs to treat CAP.

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