DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

The Honorable John D. Dingell
Chairman
Committee on Energy and Commerce
House of Representatives
Washington, D.C. 20515-6115

MAY 30 2007

Dear Mr. Chairman:

Thank you for your April 25, 2007, letter containing a follow-up question for the record from the March 22, 2007, hearing entitled, "The Adequacy of FDA to Assure the Safety of the Drug Supply – Part II," before the Subcommittee on Oversight and Investigations. Below we have reprinted the question from Representative Greg Walden in bold followed by our response.

Question

Notwithstanding the legitimate concerns that have been raised in connection with the use of non-inferiority studies to support certain product approvals, it remains that for certain conditions such as serious infections caused by resistant microbes, other study designs may be unethical and for these conditions well-designed non-inferiority trials may remain appropriate. Will changes in FDA policy concerning the agency's reliance on non-inferiority evidence take account of these considerations and will FDA continue to permit the use of such evidence in appropriate cases?

Response

Over the last few decades most antibacterial drugs have been approved based upon non-inferiority studies. Recently the use of non-inferiority studies has been called into question, for studies of less serious infectious diseases that typically resolve over time in the absence of antibacterial therapy, where the effectiveness of standard drugs compared to placebo is not well-established. In such cases, a non-inferiority study may not be informative. However, in more serious infectious diseases where antibacterial drugs are reliably known to have a large treatment effect and prevent the serious consequences of untreated infection, non-inferiority studies remain an appropriate type of study for evaluating the safety and efficacy of antibacterial drugs.

For these serious infectious diseases, e.g., acute bacterial meningitis or acute bacterial endocarditis, non-inferiority studies are both scientifically valid and an ethically acceptable

study design because in these cases, it is known that the test drug is an active treatment and would be effective in the non-inferiority study.

When considering the use of a study designed to show non-inferiority to an active comparator, it is essential to know what the effect size of a comparator would be relative to placebo in order for the non-inferiority study to be informative. It is important to carefully develop an estimate of the effect size for the active comparator treatment at the time when the study is being designed.

An active controlled study designed to show non-inferiority compares the treatment effect of a test drug with the treatment effect of an active comparator drug. The difference between the effect of the active comparator and the effect of placebo or no treatment is the effect size. When the effect size of the active comparator drug relative to placebo is reliably known, one can conclude a test drug would have been better than placebo if the test drug is non-inferior to the comparator (i.e., by demonstrating an effect for the test drug that is within a pre-determined margin relative to the effect of comparator). Essentially, the conclusion is that if A (the active comparator) is better than placebo and B is not inferior to A, then B (the test drug) is superior to placebo and therefore B is an active treatment. This approach depends upon the validity of the assumption that A would reliably beat placebo.

FDA is committed to providing advice to sponsors to establish acceptable approaches for determining non-inferiority margins in diseases where non-inferiority designs are appropriate. In some circumstances this may require a careful review and synthesis of data derived from older medical literature in order to understand the effect of treatment with an active antibacterial drug on survival or other outcomes in the disease of interest.

FDA is aware of the ethical concerns related to studying certain types of infectious diseases in placebo-controlled trials. FDA would not require a study design that we believe would compromise patient safety. However, there may still be circumstances in serious diseases where no drugs are known to be effective and for which a non-inferiority trial design would be non-informative, and therefore inappropriate. In these situations a superiority trial, e.g., either against placebo or a non-approved comparator, may be an appropriate study design.

Appropriate design of investigational studies is essential to conducting informative and ethical studies that provide for patient safety and evaluate the safety and efficacy of investigational drugs. FDA is committed to working through these important and often challenging issues.

Please let us know if there are further questions.

Sincerely,

Stephen R. Mason
Acting Assistant Commissioner
for Legislation