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By Lynne Peterson

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Stephen Snyder, Publisher
1879 Avenida Dracaena
Jensen Beach, FL 34957
772-334-7409 Fax 772-334-0856
www.trends-in-medicine.com

The FDA View of Non-Inferiority Trials

A number of drugs are in development for which the manufacturer (sponsor) hopes to use one or more non-inferiority trials for FDA approval. The fate of these drugs may hinge on the Agency's view of non-inferiority trials. Two senior FDA officials and other experts agreed to discuss the questions and issues surrounding non-inferiority trials, including Dr. Robert Temple, Director of the FDA's Office of Medical Policy, Center for Drug Research and Evaluation, as well as the Acting Director of Drug Evaluation 1 (which is in charge of oncology, neurology and cardiac drugs), and Grant Williams, Deputy Director for Division of Oncology Drug Products, Office of Drug Evaluation and Research I.

At least some FDA officials are unhappy that so much drug development effort is being focused on non-inferiority trials because it means that R&D isn't going to develop new treatments and cures. "It is a really sad state of affairs that we are seeing so many non-inferiority trials," one official said.

The FDA has the authority to require more than one trial, but it is not required to do so. Thus, it also has the authority to approve a drug based on just one non-inferiority trial, and it has done this. The FDA official said, "Non-inferiority trials are not a distinct entity. They are different, but there is no rule. The FDA regulatory interpretation is that we can demand more than one trial, but there is efficacy guidance that…talks about conditions where we could consider one trial, where the evidence is very strong, and where the (investigational drug) is better than what is out there, so it would not be ethical to deny it."

The FDA once made this comment in questions posed to its Oncologic Drugs Advisory Committee (ODAC): "In non-inferiority studies, it is important to know the size of the treatment effect of the comparator agent, and to decide on the amount of comparator effect that should be preserved when testing a new treatment. The estimate of the effect size, the amount of efficacy to be preserved, and the choice of endpoint all influence the sample size of non-inferiority studies. Sample sizes may range from several hundred to many thousands of patients, depending on the combination of factors."

There has been some internal debate at the FDA over whether the p-value for approval based on a single trial (non-inferiority or efficacy) has to be ≤ 0.00125. Speaking at a session at the American College of Cardiology this year, Ray Lipicki, former director of the Division of Cardio-Renal Drug Products at the FDA, said, "The usual standard of care (for approval) is two trials with a p-value $\leq .05$. If there is only one trial, the notion that the p-value needs to be $\leq .00125$ is one that is selling, and it makes sense." A current senior FDA official said, "I've heard more discussion of numbers at CBER than in CDER. There is no rule to that effect – just the need for strong evidence and evidence of an impact."

There are several issues with non-inferiority trials that concern the FDA, including:

The particular concerns of the FDA are that:

- **Assumptions may be made about the size of the effect of the control**, or that the trial situation is similar to the situation where the control drug worked, but, instead, the trials may have been very different clinical situations. The FDA official said, "Usually the strength of evidence is less with a non-inferiority trial because all kinds of clinical trial assumptions are made. There are assumptions inherent in non-inferiority trials, so the data is always a little tentative, and the evidence is not as strong as a superiority trial. The strength is just not there."

- **The ethical imperative may not be there.** The FDA official said, "In a non-inferiority trial you are showing, or hope you show, that you are as good as another drug, not that you are better…so what is the ethical imperative (to approve the drug on one trial)? Unless it is better in some other way – such as less toxic – it's hard to say you are withholding something."

- **Soft endpoints can be difficult to interpret.** The FDA official said, "In a setting where we are using different endpoints (other than response rate), we see situations where we are just looking at one curve and comparing it to another curve and the sponsor is saying it doesn't see a difference. Absent statistical inference, you don't know if the drug is working. So, based on one trial and two curves that look kind of similar, you could be wrong that they are the same and even wrong that the drug works…So, in one setting, we are asked to make a gamble that a drug has an effect, and in another setting, we can say we have no doubt it has a 20% response rate and there is assurance it is at least as good statistically (as the control)."

Non-inferiority trials can be easier to interpret in oncology, especially when the clinical endpoint is response rate. Then, there is less concern about whether the investigational drug really works. The FDA official explained, "Oncology trials often use response rate as an endpoint, and response rates don't occur by chance, so even without a control arm you know if you are having an effect. You need a control to see if the effect is the same as what else is out there, but the fear in that non-inferiority trial is not so great. You know whether it works."

FDA officials did not specify how large a non-inferiority trial must be, but one FDA source said the size of a non-inferiority trial is decided on a case-by-case basis, depending upon the disease setting, the active control, the effect size, etc. This source said that, generally, non-inferiority trials are larger than superiority trials.

The topic of the size of non-inferiority trials came up at a March 2003 meeting of ODAC. The FDA asked MedImmune to explain why it had not completed required post-marketing studies of Ethyol (amifostine) demonstrating nephroprotection and non-inferiority of survival or a survival surrogate. The company cited two problems: accrual issues and the number of patients required to complete a non-inferiority trial. An official complained, that a non-inferiority trial would require 2,400 patients if survival were the endpoint, and 1,150 patients if response rate were the endpoint.

How close to the comparator an active drug must be also depends on the disease setting. An FDA official explained, "If it is a curative setting, like adjuvant breast cancer, then 75%-80%, but in a non-curative setting, we have approved based on 50%…We don't look at p-values at all. We look at the confidence interval. There is no magic p-value."

EXAMPLE OF NON-INFERIORITY TRIAL

FDA officials did not directly discuss any drugs already approved, currently under review, or in development, but an FDA source pointed to Roche's Xeloda (capecitabine) as an example of a drug that was approved based on one non-inferiority trial. The following analysis of a drug in development, which is seeking non-inferiority approval help, put the FDA's more general comments in context.

ASTRAZENECA'S Exanta (ximelagatran). AstraZeneca is conducting two Phase III non-inferiority trials (SPORTIF-III and SPORTIF-V) of Exanta, an oral direct thrombin inhibitor that would compete with warfarin (Coumadin). SPORTIF-III was recently completed and the data was presented at the ACC meeting in March 2003. SPORTIF-V is ongoing, with data expected at the European Society of Cardiology meeting in September 2003 or the America Heart Association meeting in November 2003.

How does the Exanta data look from an FDA perspective? **So far, pretty strong**.

➢ **Evidence of an impact and strong data. Yes**.

SPORTIF-III was an open label, multinational trial of 3,407 patients. The trial met its primary objective -- to establish non-inferiority of Exanta for prevention of strokes (ischemic and hemorrhagic) as well as systemic embolic events based on an intent-to-treat analysis. In addition, data from the second trial, SPORTIF-V, will be included in the submission, A researcher said, "We found Exanta as effective as warfarin in preventing stroke and systemic embolic events, and it caused less bleeding than warfarin." If the results are as good or better with SPORTIF-V, this FDA test would appear to be met.

➢ **Assumptions. No.**
The clinical situations for the SPORTIF trials appear to be very similar to real-world use of warfarin, except perhaps that warfarin control might be poorer in real life, which would bias the trial in favor of the control, not Exanta. So, the trial appears to have strength.

➢ **Ethical imperative. Yes.**
Even if Exanta is not superior to warfarin in efficacy, it may offer benefits to patients. A researcher said, "We know warfarin is very effective if given well, but most patients can't tolerate it well over a long period of time…We wanted to show Exanta is at least as effective, more convenient and has less need for blood test monitoring…and it caused less bleeding than warfarin."

➢ **Soft endpoints. Yes.**
Hard, not soft, endpoints were used in the SPORTIF trials, and it is not simply a comparison of two curves.

➢ **Safety. Uncertain.**
This is always a big FDA concern and the key component of any risk:benefit analysis. There was an increased incidence (6.5%) of elevated liver enzymes (3xULN) compared to warfarin, but researchers said that in most cases the abnormalities went away when the drug was stopped or even sometimes when it was continued. There also was a hint of an increased risk of MI. Thus, the SPORTIF-V trial may be critical in assuring the FDA of the safety of Exanta.

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