

June 3, 2005

Dockets Management Branch (HFA - 305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Docket Number 2005D-0112

Request for Comments on: 2005 Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics.

Eli Lilly and Company (Lilly), as a global research based pharmaceutical company, is committed to the development of innovative medications for the treatment of cancer.

Lilly congratulates the FDA on developing this draft guidance entitled, Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics, through a process that has included public workshops of oncology experts and discussions before FDA's Oncologic Drugs Advisory Committee. This draft guidance, being the first in a planned series of cancer endpoint guidances, provides useful information and general principles on the data that will be used to support effectiveness claims in new drug applications (NDAs), biologics license applications (BLAs), or supplemental applications to treat patients with an existing cancer.

Following are suggestions that Lilly believes will enhance the clarity of the Draft Guidance. These suggestions are organized by the major sections of the Draft Guidance and line numbers are referenced for ease of review.

***CLINICAL TRIAL ENDPOINTS FOR THE APPROVAL OF
CANCER DRUGS AND BIOLOGICS***

II. Background

Lines 45-46 state, “Endpoints for later phase efficacy studies evaluate whether a drug provides a clinical benefit such as prolongation of survival or an improvement in symptoms.” Lilly believes that Health Related Quality of Life (HRQL) is an important endpoint that can be used to support approval. The FDA addresses the utility of the HRQL in later sections of the Draft guidance; however, Lilly believes it important to state this early in the Guidance. Lilly acknowledges that the FDA has relied on symptom scores, signs and symptoms as the primary evidence of effectiveness, approvals have not been based on HRQL. The use of HRQL assessments as primary efficacy endpoints to support cancer drug approval would require discrimination between tumor symptoms and the drug toxicity, especially when evidence is based on comparison to a toxic active control. This may present difficulty in assessing both general health-related HRQL instrument scales and endpoints such as time to treatment failure, which may include endpoint components affected by drug toxicity. However, HRQL measures, for which sponsors obtain FDA agreement regarding their utility, could be considered as an acceptable endpoint. Lilly also acknowledges that a discussion on HRQL will be discussed in a separate FDA draft guidance on patient-reported outcomes (PRO).

II. Background, B. Endpoints Supporting Past Approvals in Oncology

Lines 125-126 state, “Drugs approved under accelerated approval regulations must provide a benefit over available therapy.” This statement may be considered contradictory the FDA statement FDA in the July 2004 Guidance on Fast Track Drug Development Programs (III.B.1). In the July 2004 Guidance it states that “FDA recognizes that, as a general matter, it is preferable to have more than one treatment approved under the accelerated approval

provisions because of the uncertainty inherent in an approval under these conditions.” The FDA should clarify if it would grant a second accelerated approval to a new therapy that provided similar benefit to a product with an existing accelerated approval.

III. General Endpoint Considerations, B. Endpoints Based on Tumor Assessments

Lines 197-199 states, “For instance, response rate determinations in malignant mesothelioma and pancreatic cancer are often unreliable because of the difficulty in measuring these tumors with currently available imaging modalities. ” Lilly believes this statement should be clarified. As example, if investigators show 15% objective response rate (ORR) for Drug A and 30% ORR for Drug B, and independent reviewers score ORR as 10% for Drug A and 20% for Drug B and then FDA reviewers score 5% for Drug A and 10% for Drug B, should all the data demonstrating that Drug B has better ORR be considered unreliable? Lilly suggests the following revision: **“For instance, response rate determinations in malignant mesothelioma and pancreatic cancer are often unpredictable because of the difficulty in measuring these tumors with currently available imaging modalities. However, if tumor response consistently favors one treatment group, it could be relied upon to support approval.”**

III. General Endpoint Considerations., B. Endpoints Based on Tumor Assessments

1. Disease-Free Survival

Line 247-249 states, “Another issue in defining DFS is whether deaths occurring without prior documentation of tumor progression should be scored as DFS events (disease recurrences) or should be censored in the statistical analysis.” It would be helpful if FDA clarified if it insists that DFS be defined in all cases as the time from randomization until recurrence of tumor or death from any cause. If such were the case, a corresponding sensitivity analysis could be performed where deaths occurring without prior documentation of tumor progression were censored.

3. Time to Progression and Progression Free Survival (PFS)

Regarding PFS trial design issues, Lines 340 – 342 states, “It is important that methodology for assessing, measuring and analyzing PFS be detailed in the protocol and statistical analysis plan.” First, Lilly believes this advice is applicable to all the endpoints described in the Draft Guidance. Second, Lilly would consider it is acceptable for the methodology to be described in the protocol or the statistical analysis plan, thus proposes this as a revision. The FDA is asked to clarify these points.

Overall, Lilly believes that the guidance provides useful comment for sponsors.

Lilly continues to support the effort of the FDA Office of Oncology to provide guidance on clinical trial endpoints, thus advancing the science of innovation. We thank the Office of Oncology for this opportunity to comment and look forward to future public workshops and subsequent FDA guidance documents on specific tumor types.

Sincerely,

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