

April 12, 2004

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

RE: Comments on Docket No. 2004D-0035, *Guidelines for Preclinical and Clinical Evaluation of Agents used in the Prevention or Treatment of Postmenopausal Osteoporosis (April 1994)*

Dear Sir or Madam:

Wyeth Pharmaceuticals Inc. (Wyeth), hereby submits comments to **Docket No. 2004D-0035** which was published in the Federal Register, Volume 69, Number 28, pages 6673 – 6674 (February 11, 2004).

Wyeth is one of the world's largest research-based pharmaceutical companies. Wyeth is a major research-oriented pharmaceutical company with leading products in the areas of women's health care, cardiovascular disease, central nervous system drugs, anti-inflammatory agents, anti-infective agents, vaccines, biopharmaceutical and consumer healthcare products.

Wyeth acknowledges the Agency's efforts to provide further recommendations to industry for the development of studies for the preclinical and clinical evaluation of agents used in the prevention and treatment of postmenopausal osteoporosis.

In **Docket No. 2004D-0035**, the FDA requested comments on two specific questions as well as the draft guideline entitled "*Guidelines for Preclinical and Clinical Evaluation Agents used in the Prevention or Treatment of Postmenopausal Osteoporosis (April 1994)*."

Docket No. 2004D-0035 - FDA's Questions and Wyeth's Response

1. Is it appropriate to continue to use placebo controls in fracture end-point trials?

Placebo control trials provide the most accurate, scientific information for fracture end-point studies. This trial design is ethical, provided 1) vitamin D

and calcium are administered to all subjects (a well recognized therapy for bone loss); and 2) adequate escape criteria and proper follow-up are pre-defined in the protocol.

2. Do fracture end-point trials need to be as long as 3 years in duration, or could shorter studies provide adequate evidence of a new osteoporosis drug's effectiveness and safety?

Fracture end-point studies do not need to be 3 years in duration. This position is supported by evidence of competitor data (e.g., Actonel[®], [risedronate]) where fracture reduction was demonstrated at 1 year. Bone biopsies in a patient subset should be conducted at 1 year, as a demonstration of bone quality, which would also be supported by preclinical data. Assuming acceptable efficacy and safety, such data should be adequate for submission and approval of a marketing application, with trials continuing for collection of safety data. In addition, fracture trials need to be short enough to permit a placebo-controlled design and to allow for high patient retention

Guidelines for Preclinical and Clinical Evaluation Agents used in the Prevention or Treatment of Postmenopausal Osteoporosis (April 1994)

II. Clinical Studies, B. Phase II Studies

(Page 8, 1994 Guidance): Phase 2 studies should be limited to a treatment duration of 6 months. Biochemical bone markers and/or Bone Mineral Density (BMD) should be the primary endpoint(s) for such trials. Bone biopsies should not be performed during phase 2 studies.

V. Statistical Considerations, C. Data Analysis (Interim Analysis)

Conduct of an interim analysis with p-value adjustment, is appropriate for fracture end-point trials, if the treatment period were to continue beyond one year. This provides the sponsor the opportunity to determine the nature of the effect and to take appropriate action with patient safety the primary concern.

This letter is submitted in duplicate. Wyeth appreciates the opportunity to provide this constructive input to the rulemaking process. Please contact me by telephone (484) 865-3695 or via fax (484) 865-4312 if there are any questions regarding the submitted comments, or should you require additional information regarding this submission.

Sincerely,

Kathryn A. Penhale
Associate Director, Worldwide Regulatory Affairs