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

Re: Docket No. 00D-1307, CDER 67. Guidance for Industry: "Development of Parathyroid Hormone for the Prevention and Treatment of Osteoporosis" published on June 14, 2000

Eli Lilly and Company (Lilly), as a global research-based pharmaceutical company, is committed to the development of innovative medications for the prevention and treatment of osteoporosis. Lilly looks forward to the introduction of new and improved products for this purpose in the near future and to assuring that patients have appropriate access to them.

Lilly acknowledges the efforts of the Agency to provide a guidance concerning the development of parathyroid hormone (hereafter, PTH) and related peptides for the prevention and treatment of osteoporosis. Lilly has reviewed the draft guidance document published in the Federal Register on June 14, 2000, and appreciates the opportunity to provide comments.

Consideration of PTH and related peptides is of great importance to clinical medicine, because these peptides represent the only skeletal anabolic (bone formation) compounds likely to achieve wide clinical use in the near future. Over the last several decades, a substantial number of patients have received PTH for therapeutic, clinical trial, or diagnostic purposes and we are not aware of any evidence that use of PTH in humans is associated with development of osteosarcoma.

With that in mind, Lilly has several comments regarding the draft guidance. **A major concern lies in the overly restrictive definition of osteoporosis, which, if required for clinical trials and subsequent labeling of PTH and related peptides, would ultimately deny many thousands of patients a highly effective therapy for their skeletal disease.** For example, the proposed definition would require a fracture prior to therapy and a BMD of greater than or equal to -2.5 SD below the normal mean; thus precluding treatment of patients otherwise demonstrably at high risk for fractures.

00D-1307

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Answers That Matter.

Specific comments and recommendations:

IV. Clinical Studies

Lines 52-57: Lilly accepts the recommendation that treatment with PTH and related peptides be confined to adults, who by definition "have completed bone maturation." However, the restriction of therapy in clinical trials to "severe osteoporosis" is inappropriate. The patients studied in clinical trials must reflect the spectrum of disease seen in clinical practice, in order to define the benefit to risk ratio for PTH and related peptides. The consequences of the proposed definition restricting studies to "severe osteoporosis" may put needless constraints on the clinical use of PTH and related peptides. There are several points that Lilly wishes to bring to the Agency's attention in this regard.

1. **BMD cutoffs and fracture requirements are too restrictive:** The Agency's proposed BMD cutoff does not address the larger issue of clinical case-finding and risk assessment for choice of therapy. The cutoff of -2.5 SD from the young normal mean for BMD does not properly acknowledge that as BMD decreases, there is a "gradient of risk," (Melton J, Eddy D, Johnston C, *Annals of Internal Medicine*. 1990;112: 516-528) with fracture risk increasing exponentially. There is no distinct break in the risk curve at -2.5 SD, and many patients suffer fragility fractures when BMD is within the range of -1.0 to -2.5 SD below the young normal mean.

On the other hand, many patients are found to have BMD reduced more than 2.5 SD from the young normal mean, but have not yet fractured, and would be denied entrance into clinical trials under the proposed guidance. There is no question, however, that their risk of fragility fracture is very high.

This guidance, if codified in product labeling, would in many circumstances require the physician to allow the patient to suffer a first osteoporotic fracture (which dramatically increases the risk of the next fracture) before a highly effective therapy, such as PTH, could be offered.

The difficulty in using a strict hip and lumbar spine BMD cutoff is compounded by frequent discordance among BMD measurements at different skeletal sites and with different instruments. The guidance also does not acknowledge the availability of other techniques for the diagnosis of osteoporosis (e.g., ultrasound, peripheral densitometry, QCT).

2. **Alternative therapies may not be appropriate:** The Agency must also recognize that many patients may not benefit from current osteoporosis therapies. For example, patients may be ineligible for certain therapies due to contraindications or side effects such as a history of or high-risk for breast or endometrial cancer, venous thrombosis, or gastrointestinal disorders.

Additionally, there are patients who show little or no skeletal response to existing antiresorptive therapies. Patients having osteoporosis of any severity who are not candidates for existing therapies should have access to PTH and related peptide therapies.

Recommendation: Lilly believes that a rational approach is to state simply that "PTH and related peptides should be used for the treatment of adults with osteoporosis, as judged by clinically-acceptable criteria." If the Agency wished to give examples of such criteria, they might be stated as follows: "The presence of osteoporosis may be detected by bone mineral densitometry or other approved techniques, a history of fragility fracture, or physical signs of osteoporosis such as thoracic kyphosis."

IV. Clinical Studies

Lines 59-61: Lilly recommends that the exclusion statement be modified as follows: "Patients with metabolic bone diseases other than primary osteoporosis, including Paget's disease of the bone, and those with otherwise unexplained elevations of serum calcium or alkaline phosphatase (above the upper limit of normal for the laboratory), should generally be excluded from clinical trials with PTH and related peptides." This statement covers clinically relevant conditions that may be exacerbated by PTH administration or for which PTH treatment may be ineffective.

A. Patient follow up

Lines 69-72: Lilly recommends that "...long-term follow-up of patients treated with PTH in clinical trials..." should be modified to include only patients with long-term exposure to PTH and related peptides, not just any previous exposure. Many hundreds, possibly thousands, of patients have received various forms of PTH briefly for diagnostic, physiologic research, and Phase 1 clinical pharmacology studies over the last several decades, with no known severe adverse consequences. The findings of osteosarcoma have arisen only in recent long-term animal studies, and not in shorter-term animal studies, suggesting that long-term monitoring of humans given brief exposure (such as single or few doses) to PTH and related peptides is unnecessary.

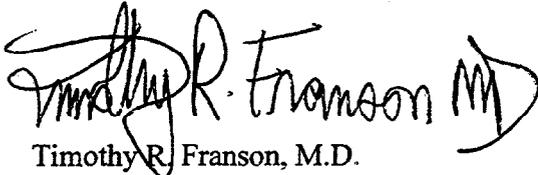
B. Patient informed consent form:

Lines 76-78: Based on the current data available, we agree with the Agency's statement on including the rat osteosarcoma findings in the informed consent documents for clinical trials, in accord with current regulations. However, we would fully expect that the need for this statement within the informed consent documents would be revisited as more human data becomes available.

Once again, Lilly appreciates the opportunity to comment on this draft guidance. We wish to maintain the highest possible level of involvement in preparation of any final guidance, and would welcome meetings with the Agency at any time to discuss our recommendations. Eli Lilly and Company looks forward to working with the FDA to ensure the availability of safe and more effective products for the prevention and treatment of osteoporosis, a common and devastating chronic disorder of our aging population.

Sincerely,

ELI LILLY AND COMPANY

A handwritten signature in black ink that reads "Timothy R. Franson M.D." with a stylized flourish at the end.

Timothy R. Franson, M.D.
Vice President
Clinical Research and
Regulatory Affairs - U.S.

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