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August 13, 2000

Re: Docket ID # 00D-1307, CDER 67.

Dear Sirs,

I have read your recent draft "Guidance for Industry" document regarding parathyroid hormone and related peptides, Docket ID # 00D-1307, CDER 67. Let me say at the outset that I applaud the FDA's efforts to be inclusive regarding the solicitation of comments regarding the future use and study of PTH. Let me also say at the outset that I have two potential dualities of interest on this subject. First, I am one of the patent holders for PTHrP. Second, I am on PTH Consultant Board for Eli Lilly Co.

Overall, I find the tone and content of the FDA "Guidance" positive and helpful, and I support almost all of the points made. Having said this, there are four points which I think should be revised.

1) While I fully concur with the summary of the rodent data regarding osteosarcoma development, and strongly support efforts to monitor the development of this theoretical complication in human studies, I do not think that the statement balances this rodent perspective with human observations. Perhaps a statement should be included such as the following: "In contrast to the rodent data, there are as yet no data to support the development of osteosarcoma in humans exposed to PTH or related peptides over prolonged periods. This includes decades of exposure of humans to PTH in the setting

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of renal failure, dialysis, parathyroid carcinoma, primary hyperparathyroidism, secondary hyperparathyroidism due to vitamin D deficiency. Similarly, humans with humoral hypercalcemia of malignancy, despite the frequency of the syndrome and the marked elevations in circulating PTHrP which occur in this syndrome, have not demonstrated a documented increase in osteosarcoma." Such a statement would provide greater balance to the statement, and strengthen the FDA's rationale for allowing human studies to continue, a position with which I am in full accord.

2) With the presentation of fracture data by Dr. Robert Neer at the Endocrine Society Annual Meeting in Toronto this past June (*Program and Abstracts, The Endocrine Society Annual Meeting, Toronto, June 2000, p. 42*), there can be little question that the increase in BMD observed by investigators in multiple studies is accompanied by an increase in anti-fracture efficacy. This contrasts with the fluoride experience, where an increase in BMD is not accompanied by an increase in anti-fracture efficacy. Thus, the guidance document should also acknowledge that the efficacy of PTH and related peptides, not only in increasing bone mass, but also reducing fracture incidence, is likely to be of significant value to patients.

3) Some discussion of duration of trials should be included. The rodent toxicity data is derived from studies which involved most of the life-span of the animals. In contrast, PTH treatment is generally employed for a maximum of two years, and substantial effects on BMD are observed at much earlier time points. A two-year treatment in a person with a life expectancy of 80 years (to keep numbers round) would be for 1/40th of the life span, a situation quite different from the rodent studies. Thus, brief duration of treatment should be a long-term goal.

This is of particular relevance in the case of PTHrP(1-36), since animal (*J Bone Min Res 15:1517-25, 2000.*) and human (*J Clin Endocrinol Metab 83:2786-2791, 1998.*) studies suggest that while it stimulates bone formation, it does not stimulate resorption under the conditions studied (single daily dosing). While these results are preliminary and need to be extended, they suggest that PTHrP may be a pure anabolic skeletal agent, and may generate increases in bone mass in time frames even more rapid than those observed with PTH.

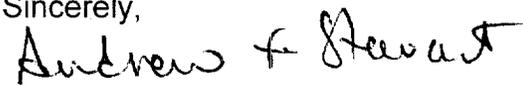
With this reasoning in mind, a statement such as the following perhaps should be included: "Given the association of duration of exposure with osteosarcoma development in rodents, human studies with PTH and related peptides should be limited in duration to the briefest duration possible, optimally less than two years, unless compelling justification is provided."

4) The requirement for a prior fracture is not reasonable, since many patients with severe osteopenia, e.g. BMD T-score values of -3.5 or greater, may not yet have developed a fracture, and yet are at enormous risk. Given the anti-fracture efficacy of PTH, it is not reasonable to exclude this large population from treatment.

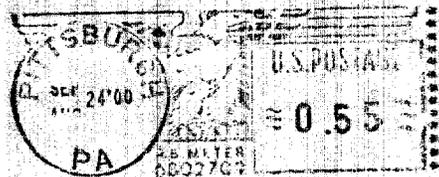
Again, in the absence of data, I would argue that the fracture requirement be stricken, and the inclusion criterion expanded to subjects with osteopenia as demonstrated by BMD T-scores of -2.0 or greater. This will allow an examination of the full range of anti-fracture efficacy of PTH, and will provide some insight, in the unlikely eventuality that osteosarcoma develop, as to the likelihood that this adverse outcome is more likely in subjects with or without pre-existing fractures.

Again, I want to thank the FDA for taking a leadership position in designing criteria for PTH clinical trial design. Please do not hesitate to contact me if there is any additional information you might require.

Sincerely,

A handwritten signature in black ink that reads "Andrew F. Stewart". The signature is written in a cursive, flowing style.

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Professor of Medicine



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