

August 11, 2000

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



**RE: [Docket No. 00D-1307]  
Draft Guidance for Industry on Development of Parathyroid Hormone for the  
Prevention and Treatment of Osteoporosis**

Merck & Co., Inc, is a leading worldwide, human health product company. Merck's corporate strategy -- to discover new medicines through breakthrough research -- encourages us to spend more than \$2 billion, annually, on worldwide Research and Development (R & D). Through a combination of the best science and state-of-the-art medicine, Merck's R & D pipeline has produced many of the important pharmaceutical products on the market today.

Research, by its nature, is a multidisciplinary and highly risk-intensive business. It depends upon many variables, including: prolific source materials, first class talent, adequate funding, efficient and effective quality processes and procedures, and a predictable regulatory environment.

Merck Research Laboratories (MRL), Merck's research division, is one of the leading U.S. biomedical research organizations. MRL tests many compounds or potential drug candidates at one time through comprehensive, state-of-the-art R & D programs. There are three main stages to Merck's R & D process: basic research or discovery, followed by developmental studies in animals and manufacturing quality assurance testing, and finally, human clinical research.

Merck's research scientists ensure that our Research process continues to identify medically important product candidates from thousands of chemical and molecular entities screened each year. Only one in ten of these research product candidates is selected to enter the Development testing programs. The medicines which Merck ultimately presents to worldwide health authorities for marketing approval are those that have met the highest technical standards available and those that are able to withstand the most critical regulatory review.

Merck supports regulatory oversight of product development that is based on sound scientific principles and good medical judgment. Regulators must be reasonable, unbiased, and efficient when they review the quality, effectiveness, and safety of our products. It is in both of our interests to see that important therapeutic advances reach patients without unnecessary or unusual delays.

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Merck has participated with health authorities from around the globe in the harmonization of regulatory standards under the auspices of the International Conference on Harmonization (ICH). The objectives of ICH have been to identify and correct unnecessary redundancies and time-consuming inefficiencies in development of pharmaceutical products caused by incompatible regulatory schemes. We continue to monitor the equitable and consistent application of these harmonized standards to product development in order to ensure that *new* or *improved* therapies reach patients as swiftly as possible.

In the course of bringing our product candidates through developmental testing and clinical trials, Merck scientists regularly address issues and/or problems affected by this proposal. Indeed, Merck has developed and obtained approval for the leading antiresorptive agent under current FDA guidelines governing development of agents for the prevention and treatment of osteoporosis. For this reason, we are very interested and well qualified to comment on this FDA guideline for the development of parathyroid hormone (PTH) for the prevention and treatment of osteoporosis.

#### **General Comments/Statement**

Merck commends the US FDA for examining the difficult issue of the carcinogenicity observed in preclinical studies with rodents, and its balanced approach to crafting a guidance which balances this serious concern by seeking to improve the risk to benefit ratio of studying PTH. The approach taken is consistent with that taken for estrogen products that have the potential to promote the growth of several types of cancer, but also have many uses in postmenopausal women where the benefits outweigh the risks. Merck supports the FDA's recommendation to limit the participation in clinical studies to adults with severe osteoporosis who have completed bone maturation, to define the meaning of "*severe osteoporosis*", and to exclude patients with Paget's disease because of their known increased risk of osteosarcoma. We agree that the risks of PTH appear to outweigh the benefits in the prevention of osteoporosis, and that it should not be developed for this indication.

#### **Specific Comments**

Other mechanistic, safety, and practical concerns are associated with PTH therapy of osteoporosis. These include not only the long-term risk of bone tumors, but also concerns regarding the quality of bone generated by anabolic therapy, the detrimental effects sometimes seen at sites rich in cortical bone, and risks associated with primary hyperparathyroidism (such as nephrolithiasis, peptic ulcer disease, and hypertension). Osteoporosis in postmenopausal women is a chronic disease which must be managed over a patient's lifetime--typically 15 years or more after diagnosis. The risks of long-term therapy with PTH and the likelihood that many patients will not accept long-term injection therapy also raises the concern of how to preserve PTH-associated gains in bone mineral density (BMD) after discontinuation of PTH therapy. Real-world use is thus likely to occur in combination with anti-resorptive agents, either during short-term PTH therapy and/or following such therapy. PTH may prove useful in the treatment of glucocorticoid-induced osteoporosis (GIOP).

The following comments suggest ways that this guidance may be broadened to set standards for addressing these additional safety and mechanistic concerns. The suggestions include limiting PTH treatment duration both in clinical trials and the resulting indication, defining appropriate treatment monitoring and follow-up, setting clinical trial design and endpoint standards consistent with those of other osteoporosis agents, and acknowledging the need for combination therapy studies and indications.

#### **IV. CLINICAL STUDIES** (lines 50 - 61)

***Recommendation 1:*** After line 61, add:

'Clinical trials should be designed so that patients receive preferably one year, and no more than two years of PTH therapy with a total of at least three years of follow-up (ie. 1-2 years follow up following PTH discontinuation). The sponsor should provide a strong rationale for its choice of the duration of active therapy with PTH. Even when active therapy with PTH lasts only one year (with, for example, no treatment beyond optimal nutrition, including calcium and Vitamin D, in the second and third years), three-year fracture incidence should be the primary fracture endpoint, consistent with the current FDA osteoporosis guidance. The studies should be sufficiently powered to allow an examination of the consistency of effect on fracture incidence, during the on-treatment and post-treatment periods of study. Bone biopsies should be obtained at the termination of treatment with PTH. Patients should be carefully monitored for fractures, bone tumors, hypercalcemia, nephrolithiasis, nephrocalcinosis, peptic ulcer disease and metastatic calcifications. The clinical trials should incorporate measurements of serum calcium 1-4 hours following PTH injection, since daily transient increases in serum calcium could clearly predispose to abnormal soft tissue calcification. Trial designs should incorporate a non-PTH (eg., anti-resorptive) agent, either in combination throughout the trial, or sequentially, after the completion of the active PTH treatment phase. When the PTH regimen studied includes concomitant therapy with another agent, the combination should be shown to have additional benefit (either efficacy or safety) in the treatment of severe osteoporosis beyond that of either agent administered alone. The approved indication should be based on the clinical trial design and its observed outcomes; the indication should reflect the limited duration of active therapy as well as the manner in which concomitant or sequential therapy was administered.'

***Rationale:*** The typical duration of treatment in most PTH studies to date has been 1 or 2 years. This time frame is reasonable because it balances the gains in BMD that can be achieved in this short time frame with the theoretical risk of osteosarcoma and other safety issues during longer term use and the difficult prospect of taking injections for longer than this period of time. However, osteoporosis is a chronic disease, and an anti-fracture effect which does not persist for at least three years is of limited clinical utility. In addition, questions relating to risk of bone tumors and the quality of bone generated by this anabolic therapy, mandate that the total follow-up should at least satisfy the current guidelines for new chemical entities for the treatment of osteoporosis(ie., at least 3 years).

It is widely believed that PTH will be used in the clinic in combination (either concomitantly or sequentially) with an anti-resorptive agent, in part because of the issues outlined above: a) long-term use is likely to correlate with an increased theoretical risk for bone tumors; b) the increase in BMD and fracture risk reduction may be sufficiently large during one to two years of treatment, that patients may no longer be considered "severely osteoporotic;" c) patients are unlikely to accept injections for a long period of time for a disease that is often silent and for which other effective and more convenient therapies exist; d) PTH therapy preferentially increases the density of trabecular bone and in some instances has resulted in detrimental effects at sites rich in cortical bone; e) other toxicities may exist with chronic PTH therapy (hypertension, peptic ulcer disease, hypercalcemia, metastatic calcification; nephrolithiasis, myopathy); and f) anti-resorptive agents will be required over the long term to consolidate/preserve the gains achieved with PTH and prevent bone loss that would inevitably ensue after discontinuation of PTH. Moreover, since the risk of osteosarcoma appears to be related to the underlying rate of bone turnover, being highest in children and Paget's patients in whom turnover is much higher than in healthy adults, it seems probable that the risk of such tumors would be highest in patients treated with unopposed PTH, and might be lower in those in whom an effective antiresorptive reduced the degree to which bone turnover was increased by PTH.

If a clinical development program employs a finite course of PTH therapy (eg. 1 year) for the above reasons, a full 3 years total follow-up with fracture endpoints is required to demonstrate fracture risk reduction, consistent with current FDA guidelines for agents used in the treatment of osteoporosis. One year alone of PTH therapy will not prevent post-treatment BMD loss or reduce fracture risk indefinitely. When a second agent with an anti-resorptive effect is used, either concurrently or sequentially, during this three-year period observation, there must be a demonstration that the combination adds to the efficacy of either agent administered alone. While this adds to the size and complexity of the study, it is the only way to demonstrate efficacy for the combination regimen.

Bone biopsies should be required because myelofibrosis may precede malignant changes and there is the potential that unopposed PTH may result in woven rather than lamellar bone formation, as well as increased cortical porosity, either of which would be expected to impair bone quality.

**Recommendation 2:** Omit the phrase "Prevention and" from the Guidance title.

**Rationale:** Lines 53-57 of the Guidance, by recommending that only patients with severe osteoporosis be studied. This recommendation confines the study population to a treatment, rather than a prevention, population. Merck agrees that risk/benefit considerations properly restrict PTH to the treatment of severe osteoporosis, rather than prevention.

**Conclusions**

FDA's proposed Draft Guidance for Industry on Development of Parathyroid Hormone for the Prevention and Treatment of Osteoporosis has admirably addressed the difficult subject of limiting the potential risk represented by findings of carcinogenicity potential in multiple rodent species. Expansion of this guidance is desirable to address additional risk/benefit issues and to ensure that a common standard for demonstration of efficacy is applied to osteoporosis treatment therapies with different in mechanisms. Limitation of the duration of PTH treatment, plus utilization of appropriate post-PTH therapy to maintain short term BMD gains, bone biopsies, and 3-year fracture endpoints (regardless of duration of active treatment) will help to ensure patient safety and maximize benefit for the severely osteoporotic patient.

We welcome the opportunity to comment on this Guidance and, if appropriate, to meet with you to discuss these issues.

Sincerely,  
*Nicole Sticker for*  
*Bonnie J. Goldmann*

Bonnie J. Goldmann, MD  
Vice President  
Regulatory Affairs

Attachment

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# Guidance for Industry

## Development of Parathyroid Hormone for the Prevention and Treatment of Osteoporosis

### *DRAFT GUIDANCE*

**This guidance document is being distributed for comment purposes only.**

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit comments to Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document contact Eric Colman at 301-827-6371.

**U.S. Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research (CDER)  
May 2000**

# Guidance for Industry

## Development of Parathyroid Hormone for the Prevention and Treatment of Osteoporosis

### ***DRAFT GUIDANCE***

*Additional copies of this Draft Guidance are available from:*

*Office of Training and Communications  
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Drug Information Branch, HFD-210  
Center for Drug Evaluation and Research  
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Rockville, MD 20857  
(Tel) 301-827-4573*

*Internet: <http://www.fda.gov/cder/guidance/index.htm>*

**U.S. Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research (CDER)  
May 2000**

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## Guidance for Industry<sup>1</sup>

### Development of Parathyroid Hormone for the Prevention and Treatment of Osteoporosis

*If you plan to submit comments on this draft guidance, to expedite FDA review of your comments, please:*

- *Clearly explain each issue/concern and, when appropriate, include a proposed revision and the rationale/justification for the proposed change.*
- *Identify specific comments by line number(s); use the PDF version of the document, whenever possible.*

#### I. INTRODUCTION

This guidance document provides recommendations for sponsors of new drug applications (NDAs) on clinical trials and drug development programs designed to evaluate the safety and effectiveness of parathyroid hormone (PTH) in the prevention and treatment of osteoporosis. This guidance applies to any form of PTH, including all analogs and related drug substances (e.g., PTHrP).

#### II. BACKGROUND

In preclinical studies previously submitted to the Agency, two strains of rats and one strain of mice developed osteosarcomas when given PTH and related peptides from weaning to 18 months of age. Osteosarcomas occur very rarely in mice and rats and were not observed in the control animals in these studies. Many of the tumors were discovered by direct palpation and were often metastatic at the time of discovery, suggesting that they had been present for a long time. Since rodent life expectancy is about 2 years, the animals in these studies were exposed to PTH for most of their life spans. In some cases, tumors occurred in animals at exposures (AUC) equivalent to those commonly used in clinical studies of PTH in the treatment and/or prevention of osteoporosis.

The clinical relevance of these animal findings is not currently known. This guidance was developed by FDA to clarify the Agency's current thinking regarding the impact of these preclinical findings on drug development programs for PTH for the treatment and/or prevention of osteoporosis.

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<sup>1</sup> This guidance has been prepared by the Division of Metabolic and Endocrine Drug Products in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration. This guidance document represents the Agency's current thinking on the use of parathyroid hormone in the prevention and treatment of osteoporosis. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statutes, regulations, or both.

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### **III. PRECLINICAL STUDIES**

As a result of the concern about carcinogenicity discussed above, studies to evaluate carcinogenic potential should generally be done for PTH and related peptides. These studies may entail unique design features; therefore, considerations to address these concerns should be discussed with the review staff in the Division of Metabolic and Endocrine Drug Products prior to initiation.

### **IV. CLINICAL STUDIES**

Given the uncertain clinical relevance of the findings in rodents, and in an effort to improve the benefit to risk ratio of PTH, it is strongly recommended that participation in clinical studies be limited to adults with severe osteoporosis who have completed bone maturation. For the purposes of this recommendation, *severe osteoporosis* is defined as a lumbar spine or hip T-score of <-2.5 and the presence of at least one clinically manifest, radiographically documented osteoporotic fracture at baseline prior to PTH treatment.

Persons with known Paget's disease of the bone or with otherwise unexplained elevations of plasma alkaline phosphatase (above the upper limit of normal for the laboratory) should be excluded because of the known association between Paget's disease and osteosarcoma.

#### **A. Patient Follow Up**

Any case of osteosarcoma (or other bone tumor) that develops in a study participant receiving PTH or with previous exposure to PTH should be immediately reported to the drug sponsor and the FDA.

In order to improve the ability to conduct long-term follow-up of patients treated with PTH in clinical trials, sponsors are encouraged to collect unique identifiers (e.g., name, Social Security number) for those study participants who provide their consent, when consistent with local regulations and statutes.

#### **B. Patient Informed Consent Form**

Sponsors should include information in the informed consent form about the occurrence of osteosarcomas in rodents and are requested to submit these consent forms to FDA's Division of Metabolic and Endocrine Drug Products for review.

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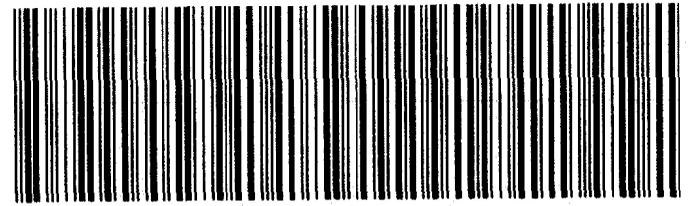
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