



P&G Pharmaceuticals, Inc.
Health Care Research Center
8700 Mason-Montgomery Road
Mason, OH 45040
www.pg.com

April 12, 2004

Division of Dockets Management
HFA-305
Food and Drug Administration
5630 Fishers Lane, rm. 1061
Rockville, MD 20852

Re: Docket No. 2004D-0035
Draft Guidance for Industry on the Preclinical and
Clinical Evaluation of Agents Used in the Prevention
or Treatment of Postmenopausal Osteoporosis;
Request for Comments

Dear Sir or Madam:

Reference is made to the Draft Guidance for Industry on the Preclinical and Clinical Evaluation of Agents Used in the Prevention or Treatment of Postmenopausal Osteoporosis (April 1994). Submitted herewith, are comments from Procter & Gamble Pharmaceuticals regarding the draft guidance document. We appreciate the opportunity to respond to the Agency's request for comments.

Regarding the 2 specific questions put forth by FDA in the request for comments:

Is it appropriate to continue to use Placebo controls in fracture endpoint trials?

- Yes. Fracture trials are the only way to definitively prove efficacy. Sample sizes required to show fracture equivalence or non-inferiority are prohibitively large, therefore placebo control studies will expose fewer patients to a risk of fracture.
- Since equivalence trials lack the negative control required for internal validity, they are not a good choice for the initial demonstration of effectiveness of a new agent.
- In order to minimize the number of patients in placebo-controlled trials, we believe high risk patients (with established osteoporosis) could be studied and an "any fracture" endpoint considered to keep studies smaller and to potentially demonstrate reduction in osteoporotic-fractures within 1 or 2 years. In such a design the total number of fractures that would occur in the placebo group to demonstrate efficacy would be no greater than the number of



fractures that you would need to observe to demonstrate efficacy in a much larger study of low risk patients.

- If an “any fracture” endpoint is adopted, the approved product would be indicated for reduction in osteoporosis-related fractures. Additional labeling claims for individual osteoporosis sites would only be permitted if they are appropriately specified in subsequent step-down statistical analyses.
- If placebo-controlled studies are conducted with these higher risk patients and demonstrate efficacy within the 1 or 2 year period, the placebo patients could be switched to an open label treatment arm more rapidly. Separately, longer term placebo-controlled studies can be run in lower-risk patients with a BMD endpoint to gather extended safety data.

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

- Assuming strong nonclinical data showing good bone quality, we agree that 2 year trials would be adequate to demonstrate efficacy, however the fracture studies should be designed to prospectively evaluate the effect of fracture reduction both at 1 and 2 years. Evaluation of the rate of loss of pharmacodynamic effect (BMD, BTM) should be evaluated for 1 year after treatment is withdrawn.
- Regarding safety for drugs intended for chronic use (>2 years or more), the requirement to gather a total of 3 years of drug exposure prior to approval should be maintained. In order to minimize the risk of fracture for high-risk patients, the required longer-term safety data may be obtained from separate placebo-controlled clinical studies in low risk osteoporotic patients using a BMD endpoint. Bone quality should be demonstrated in these studies based on bone biopsies showing histologically normal bone after 3 years of treatment. Post-approval commitments to extend ongoing studies or carry out new studies of up to 5 years duration should be considered for chronically administered agents in low-risk patients.

Comments on the specific sections of the Draft Guidance from 1994:

Preclinical Evaluation

The section should be renamed ‘Nonclinical’ as opposed to ‘Preclinical’. The pivotal nonclinical long-term efficacy/bone safety studies are typically run in parallel with the Phase III clinical trials.

The Nonclinical section should be revised to incorporate advances made in models and measurement techniques during the 10 years since the initial Guidance Document was developed. Also, the initial document focused primarily on anti-resorptive therapies. Changes need to be considered that better encompass newer/different therapies such as bone anabolics.

I. Introduction

Should be revised to reflect changes in the rest of the Nonclinical section.



II. Study Design

(p. 3) Since the Agency accepts either a prevention or a treatment study to support either indication, this should be stated.

(p. 3) Treatment Schedule: for intermittent dosing, the requirement to match the treatment schedule to that of the clinical dosing schedule based on bone turnover should be revised. Since the turnover cycle is shorter in animals, dosing to support weekly dosing in humans would result in animals being dosed every 2-3 days. Similar dosing intervals should be employed, and this would also allow a better match with data from toxicity studies with dosing intervals that match clinical dosing. Also, dose levels should be selected based on clinical relevance as well as 'optimally effective' for the animal model.

(p. 3) Treatment Duration: some newer therapies may not be given long-term to humans, for example bone anabolics such as PTH. A shorter treatment duration in the pivotal nonclinical studies should be considered for such therapies.

(p. 3) For drugs already approved for daily dosing, additional efficacy studies in animals should not be required to support intermittent or cyclical dosing in humans if the Sponsor provides justification. Additional toxicity studies with intermittent/cyclical dosing may be necessary and should be discussed with the Division to support a change in dosing regimens (e.g. daily dose change to monthly dose).

(p. 3) While bone strength should not decrease with increasing BMD, the need to show positive correlation of changes in bone mineral density (BMD) with bone strength should be revised or deleted. The relationship of BMD to bone strength measurements can vary depending on anatomic location, bone compartment (cortical, cancellous or mixed) and changes in architecture and/or bone material properties. Also, evidence from clinical and nonclinical studies that increases in BMD account for only a small part of increases in bone strength or decreases in fracture risk. Other parameters of bone quality such as architecture and material properties are believed to be equally if not more important than BMD. The wording should reflect testing requirements to demonstrate a maintenance of or improvement in (lack of detrimental effects) the primary end-point parameters of bone quality/bone strength in that study (which would be predetermined in discussions with the Agency).

III. Animal Models

(p. 3) The choice of animal models to be used should be left to the discretion of the Sponsor (with agreement from the Agency), rather than specified by the Agency. For example: "Studies on bone quality should be conducted in two bone loss models, one in rodents (predominantly modeling species), and one in a remodeling species (e.g., ...). Since the indication sought is for treatment of postmenopausal osteoporosis, models of bone loss induced by ovariectomy/estrogen-deficiency are preferred". In addition, studies in normal animals may also be appropriate to mimic low turnover osteoporosis.

IV. Biochemical Markers of Bone Turnover

(p. 4) The current text suggests urinary pyridinium cross-links and serum bone-specific alkaline phosphatase. Biochemical markers are frequently unreliable and not predictive in animals, and are not validated for all animal models. Most markers available for humans do not work or are not



available for animals. Thus, use of markers should be optional rather than mandatory. If they are used, wording should be flexible enough to allow inclusion of newer (current and future) more specific markers if available, for example urinary NTX as a resorption marker.

V. Bone Mass/Density Measurement

(p. 4) Measurement of bone ash is now outdated and superseded even for small animals. It should be made an option, but not recommended. More emphasis should be put on newer methods such as DEXA and pQCT/QCT.

VI. Analysis of Bone Architecture/Histology

(p. 5) Newer techniques such as pQCT and micro-CT that can assess 3D architecture and volume of trabecular and cortical bone in vitro and vivo should be included. Based on clinical and nonclinical data, these data provide a link to better understand changes in BMD as measured by DEXA, as well as being a better predictor of changes in bone strength than the 2D structural data generated by histomorphometry.

(p. 5) In vitro cytochemistry is (e.g., tartrate resistant acid staining for osteoclasts) needs special tissue handling and preparation to provide reliable data. Such techniques should be optional.

VII. Biomechanical Testing of Bone Strength

(p. 5) Newer techniques have been developed to measure true changes in material properties as well as bone performance under dynamic loading conditions (fatigue testing). These techniques should be included as optional methods for further demonstrating bone biomechanical property equivalence. Such techniques include micro- and nano-indentation which provide material property measures. Computational methods, such as finite elemental modeling/analysis (FEM/FEA) have been successfully used to augment 3D architectural data to predict mechanical properties and demonstrate potential mechanical benefits of alterations in trabecular architecture.

VIII. Regulatory Aspects

(no comment)

Clinical Evaluation

I. Introduction

(p.6) The division of involutional osteoporosis into two separate syndromes (Type I and Type II) has not proved to be a useful concept in the osteoporosis scientific community and has not been an aspect in study design and product labeling. Instead, a description of osteoporosis in terms of risk of vertebral and nonvertebral fractures may be more useful. For example, this section could discuss the concept of established osteoporosis (low BMD with a prevalent fracture) compared to low BMD without a prevalent fracture as two distinct populations with different risk factors for future fracture.

(p.7) 4th paragraph - Suggest additional wording (underlined) be added to last sentence: 'For example, the relationship between BMD and fracture risk has been validated only for patients receiving estrogens, and for several approved bisphosphonate drug products, and does not apply to patients receiving fluoride, SERMS, unapproved bisphosphonates, or other classes of anti-resorptive or anabolic drug products.' Current research indicates that changes in BMD produced



with antiresorptive agents (raloxifene¹, alendronate², risedronate³) do not fully explain the antifracture effect of these compounds supporting the need to demonstrate antifracture efficacy. In addition, assessment of vertebral fracture in intact vertebrae as compared to previously deformed vertebrae should be the primary endpoint.

II. Clinical Studies

(p. 8) B. Phase II Studies, 1st paragraph

For anti-resorptive drugs, the discussion of biochemical markers should address the suppression of bone turnover markers and degree to which suppression should be maintained throughout the dosing interval chosen.

(p. 8) Point #5

This point indicates that bone biopsies should be done at the end of the study. Please comment that either paired biopsies or endpoint biopsies would be acceptable, as has been the practice.

(p. 9) c. Phase III Studies

Overall, we confirm our agreement with the 1994 guidance that fracture trials are required for approval of new, non-estrogen agents. Once fracture efficacy has been demonstrated for a specific agent, only then can BMD be considered an adequate surrogate endpoint for related indications. There is not a linear correlation between BMD and fracture reduction.^{4,5} As discussed at the September 2002 Endocrinologic and Metabolic Drugs Advisory Committee meeting, there has recently been a bisphosphonate trial that has seemingly been adequately powered to show antifracture effect in which a bone density change was noted, and yet the antifracture effect was not seen. Class extrapolations should not be made.

(p. 9) The guidance should be updated with respect to anabolics agents. New anabolic agents should be required to evaluate their therapy in patients who have been previously exposed to a bisphosphonate since few potential patients would be bisphosphonate naive. Duration of previous bisphosphonate therapy and length of time since its discontinuation may be important factors to consider in study design.

(p. 10) With reference to glucocorticoid-induced osteoporosis, the guidance should also allow for treatment or prevention indications for osteoporosis that results from other forms of drug therapy (e.g. treatment with an aromatase inhibitor).^{6,7}

(p. 11) b. Study population

Suggest expanding prevention population to 1-5 years postmenopausal to reflect the duration of the postmenopausal rapid bone loss phase. This would also be consistent with the European guidelines for the prevention population.

III. Study Duration and Assessment of Efficacy

(p. 11) The preferred patient population to study should be patients with low BMD with one or more fractures. Studying this high risk population will make it easier to demonstrate fracture efficacy, and minimize the number of patients exposed to placebo.

(p. 11) Modify requirements to state that for drugs intended for chronic use (>2 years or more), placebo-controlled fracture studies should be designed to prospectively evaluate the effect of



fracture reduction at 1 and 2 years. Approval will be dependent on showing fracture efficacy and safety after at least 2 years of treatment. In order to minimize the risk of fracture for high-risk patients, the required longer-term safety data may be obtained from separate clinical studies in low risk osteoporotic patients using a BMD endpoint. Post approval commitments to extend ongoing studies or carry out new studies of up to 5 years duration should be considered for chronically administered agents in low-risk patients.

(p. 11) In addition to clinical fracture efficacy and safety data, drug approval should continue to be dependent on preclinical studies showing no detrimental effect on bone quality.

(p. 11) Delete the option that approval can be based on showing of a trend ($p < 0.2$) toward decreased fracture reduction. Given that there are now several treatment options based on demonstrated statistically significant reduction in fractures, any new agent must also demonstrate a statistically significant fracture reduction.

(pp. 13-15) This section describes various options for measuring bone mass. DEXA should be emphasized here, as it is the method most often utilized and accepted.

(pp. 15-16) Bone turnover markers - This section should mention urinary NTX and CTX as bone resorption markers.

(p. 15) Consider applying new technologies such microCT or microMRI to bone biopsy samples to determine the effect of the drug on bone quality such three-dimensional bone volume, trabecular number, trabecular thickness, trabecular connectivity, cortical thickness, etc. Bone biopsy samples could also be used to determine bone mineralization and its distribution using X-ray microradiography or similar technologies.

(p. 15) Excessive suppression of bone turnover may lead to accumulation of microdamage and thus attenuate the therapeutic effect and potentially increase bone fragility. It is therefore important to demonstrate that some level of ongoing bone turnover is evident. At minimum, single tetracycline labels should be present in biopsy specimens.

(p.15) Calcium balance studies are not done anymore in a context of a clinical trial and should be removed from guidelines.

IV. Procedure and Evaluation

(p. 17) c. Assessing fractures, 1st paragraph

Recommends that vertebral fractures should be determined by both morphometric and qualitative radiologic assessments and greater weight should be given to morphometric measurements. Based on experience with several approved products, semi-quantitative assessments of radiographs using procedures such as the Genant Scoring method should be given equal or greater weight than quantitative morphometry measurements, especially if confirmed by independent trained radiologists.⁸

(p. 17) c. Assessing fractures, 2nd paragraph

The primary assessment of incident fractures should be new fractures in previously undeformed (intact) vertebrae. Worsening of previously deformed vertebrae can be reported separately but



should not be combined in this primary assessment, since it is more difficult to detect a worsening fracture and this measure has not been used or reported for many of the previous approvals.

(p. 17) c. Assessing fractures, 3rd paragraph

It is not critical that the reader is blind to the temporal sequence of the films, provided that the reader is blind to treatment group assignment for all radiographs. Blinding to the sequence increases the risk of errors.

(p. 19) Data Analysis

Consideration should be given to a composite fracture endpoint (osteoporosis-related vertebral or nonvertebral fractures) as the primary endpoint for fracture trials. This may reduce the sample size necessary to demonstrate fracture efficacy. In this case the approved product would be indicated for reduction in osteoporosis related fractures. Labeling could separately specify osteoporosis sites, if they are appropriately specified in secondary step-down statistical analyses.

V. Statistical Consideration

(p.18) Study Design

Active control studies are not feasible for fracture endpoint studies. It is too difficult to set a non-inferiority or equivalence margin and such designs risk approval of inactive treatments.

VI. Safety Testing

(p. 20) The guidance should address bone health and long term administration of treatment.

VII. Guide to FDA Action on NDA for Osteoporosis *(no comment)*

VIII. Issues Related to Testing of Combined Drug Regimens *(no comment)*

IX. Research Priorities in Postmenopausal Osteoporosis

(p. 22) Point #1

While we agree that priority should be placed on convenient assay methods for routine determination in clinical trials, it is important to clearly distinguish between assays intended to evaluate risk of osteoporotic fracture prior to initiation of treatment, from those intended to evaluate reduction in risk of fracture due to treatment. For example, the surrogate of bone mineral density measured by DXA is an excellent tool for evaluation of risk of fracture (e.g. diagnosis), whereas it's utility for evaluation for reduction of risk of fracture while on therapy is considerably less certain, explaining less than 30% of the observed vertebral risk reductions observed with raloxifene¹, alendronate², and risedronate³.

(p 22) Point #1

We disagree that correlation of changes in biochemical markers with overall changes in skeletal mass is appropriate. The correlation should not be between surrogates (e.g. markers and bone mass) but between surrogate (marker) and the clinically important endpoint (fracture).

X. References

(no comment)



Thank you for the opportunity to provide comments. Please contact me if you have any questions.

Sincerely,

Gary F. Galletta, Pharm.D.
U.S. Regulatory Affairs
Phone: 513-622-4952
Fax: 513-622-5369

-
- 1 Sarkar S, Mitlak BH, Wong M, Stock JL, et al. Relationships between bone mineral density and incident vertebral fracture risk with raloxifene therapy. *J Bone Miner Res.* 2002;17(1):1-10.
 - 2 Cummings SR, Karpf DB, Harris F, Genant HK, et al. Improvement in spine bone density and reduction in risk of vertebral fractures during treatment with antiresorptive drugs. *Am J Med.* 2002;112(4):281-9.
 - 3 Li Z, Meredith MP, Hoseyni MS. A method to assess the proportion of treatment effect explained by a surrogate endpoint. *Stat Med.* 2001;20(21):3175-88.
 - 4 Li Z, Meredith MP. Exploring the relationship between surrogates and clinical outcomes; Analysis based on individual patient data versus meta-regression on group-level summary statistics. *J Biopharm Stat.* 200;13:773-788.
 - 5 Watts NB, Cooper C, Lindsay R, et al. The relationship between changes in bone mineral density and vertebral fracture risk associated with risedronate is not one wherein greater increases in bone mineral density relate to greater decreases in fracture risk. *J Clin Densitom.* 2004 (in press).
 - 6 Plunkett TA, Rubens RD. Bisphosphonate therapy for patients with breast carcinoma. *Cancer (suppl).* 2002;97:854-7.
 - 7 Pfeilschifter J, Diel IJ. Osteoporosis due to cancer treatment: pathogenesis and management. *J Clin Oncol.* 2000;18:1570-93.
 - 8 Genant HK, Wu CY, Van Kuijk C, et al. Vertebral fracture assessment using a semiquantitative technique. *J Bone Min Res* 1993;8:1137-47.